PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re United States Patent No. 6,083,953 Attn: Box Patent Ext.

Inventors: Nestor et al.

Issue Date: July 4, 2000

For: 2-(2-AMINO-1,6-DIHYDRO-6-OXO-PURIN-9-YL)METHOXY-1,3-PROPANEDIOL DERIVATIVE

APPLICATION FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. §156

Nutley, New Jersey 07110
May 23, 1998

Assistant Commissioner for Patents
Washington, D.C. 20231

S i r:

Pursuant to 35 U.S.C. § 156, Syntex (U.S.A) LLC, (hereinafter "SYNTEX"), a corporation organized under the laws of the State of Delaware and owner of U.S. Patent No. 6,083,953 by succesion in interest to the ownership of Syntex (U.S.A.) Inc. as reflected in assignments recorded on October 12, 1994 at reel 7162, frame 0473 and on October 18, 1999 at reel 010419, frame 0472, submits this Application for extension of its term.

Applicants seek extension of the term of U.S. Patent No. 6,083,953 for 226 days from July 28, 2014 to and including March 11, 2015, and certification that it is entitled to the rights derived from this patent as set forth in 35 U.S.C. § 156(b).

U.S. Patent No. 6,083,953
Issue Date: July 4, 2000

The information contained in this document and its Exhibits is provided in accordance with 35 U.S.C. § 156(d) and 37 C.F.R. § 1.740 and is listed in the manner set forth in § 1.740.

(1) A Complete Identification Of The Approved Product As By Appropriate Chemical And Generic Name, Physical Structure Or Characteristics

The approved product, having the trademark Valcyte™ (valganciclovir hydrochloride tablets), contains valganciclovir hydrochloride as the sole active ingredient. Valganciclovir hydrochloride is a purine derivative having antiviral activity. Specifically, valganciclovir hydrochloride is the hydrochloride salt of the L-valyl ester of ganciclovir. Valganciclovir is available as a 450 mg tablet for oral administration. Each tablet contains 496.3 mg of valganciclovir hydrochloride(corresponding to 450 mg of valganciclovir), and the inactive ingredients microcrystalline cellulose, povidone K-30, crospovidone, and stearic acid. The film-coat applied to the tablets contains Opadry Pink®.

A copy of the approved product label is annexed as Exhibit A.

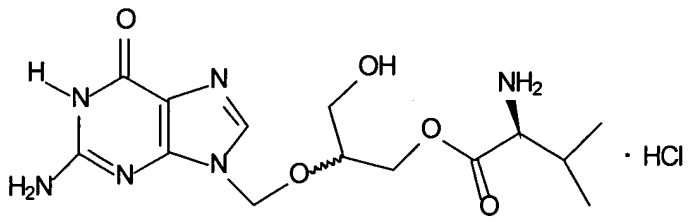
"Valganciclovir hydrochloride" is the non-proprietary name approved by the USAN council for the active ingredient in Valcyte™ Tablets.

Valganciclovir hydrochloride, has the following chemical name:

2-(2-amino-1,6-dihydro-6-oxo-purin-9-yl)methoxy-3-hydroxy-1-propanyl-L-valinate hydrochloride, or alternatively, L-Valine, 2-[(2-amino-1,6-dihydro-6-oxo-9H-purin-9-yl)methoxy]-3-hydroxypropyl ester, monohydrochloride.

U.S. Patent No. 6,083,953
Issue Date: July 4, 2000

Valganciclovir hydrochloride has the following structural formula:



The approved therapy for the approved product is the treatment of cytomegalovirus (CMV) retinitis in AIDS patients.

The term "approved product" is defined in 35 U.S.C. § 156(a) as the "product" referred to in paragraphs (4) and (5) of subsection (a). In turn, the word "product" is defined in 35 U.S.C. § 156(f)(1)(A) to comprise a "drug product" which is described in 35 U.S.C. § 156(f)(2) to include "the active ingredient of a new drug . . . including any salt or ester of the active ingredient, as a single entity or in combination with another active ingredient." The approved product subject to this Application, Valcyte™ tablets, thus includes valganciclovir hydrochloride and any salts and esters thereof, as its active ingredient, as a single entity or in combination with another active ingredient.

(2) A Complete Identification Of The Federal Statute Including The Applicable Provision Of Law Under Which The Regulatory Review Occurred

The regulatory review occurred under Section 505 of the Federal Food, Drug and Cosmetic Act ("FD&C Act"), 21 U.S.C. § 301 *et seq.*

(3) An Identification Of The Date On Which The Product Received Permission For Commercial Marketing Or Use Under The Provision Of Law Under Which The Applicable Regulatory Review Period Occurred

Valcyte™ was approved by the Food and Drug Administration ("FDA") for commercial marketing or use under Section 505 of the FD&C Act on March 29, 2001. A copy of the FDA approval letter is annexed hereto as Exhibit B.

(4) In The Case Of A Drug Product, An Identification Of Each Active Ingredient In The Product And As To Each Active Ingredient, A Statement That It Has Not Been Previously Approved For Commercial Marketing Or Use Under The Federal Food, Drug, And Cosmetic Act, The Public Health Service Act, Or The Virus-Serum-Toxin Act, Or A Statement Of When The Active Ingredient Was Approved For Commercial Marketing Or Use (Either Alone Or In Combination With Other Active Ingredients), The Use For Which It Was Approved, And The Provision Of Law Under Which It Was Approved

The sole active ingredient in the approved product is Valganciclovir hydrochloride, which active ingredient has not been previously approved for commercial marketing or use under the FD&C Act, The Public Heath Services Act or the Virus-Serum-Toxin Act.

(5) A Statement That The Application Is Being Submitted Within The Sixty Day Period Permitted For Submission Pursuant to 37 C.F.R. § 1.720(f) And An Identification Of The Date Of The Last Day On Which The Application Could Be Submitted

This application is being submitted within the permitted sixty (60) day period, the last day of which is May 27, 2001.

(6) A Complete Identification Of The Patent For Which An Extension Is Being Sought By The Name Of the Inventor, The Patent Number, The Date Of Issue, And The Date of Expiration

The complete identification of the patent for which an extension is being sought is:

Inventor(s):	John J. Nestor Scott W. Womble Hans Maag Charles A. Dvorak Paul R. Fatheree
Patent No:	6,083,953
Issue Date:	July 4, 2000
Expiration Date:	July 28, 2014 (without extension)

(7) A Copy Of The Patent For Which An Extension Is Being Sought, Including The Entire Specification (Including Claims) And Drawings

A copy of U.S. Patent No. 6,083,953 is annexed as Exhibit C.

(8) A Copy Of Any Disclaimer, Certificate Of Correction, Receipt Of Maintenance Fee Payment, Or Reexamination Certificate Issued In the Patent

No such documents have issued. A request for correction has been filed to correct the erroneous omission of two inventors' names from the issued patent. The appropriate Certificate of Correction has not yet issued.

(9) A Statement That The Patent Claims The Approved Product Or A Method Of Using Or Manufacturing The Approved Product, And A Showing Which Lists Each Applicable Patent Claim And Demonstrates The Manner In Which Each Applicable Patent Claim Reads On The Approved Product Or Method Of Using Or Manufacturing The Approved Product

United States Patent No. 6,083,953 claims the approved product or a method of making or using the approved product in claims 1-6.

Claims 1 and 2 read as follows:

1. The compound 2-(2-amino-1,6-dihydro-6-oxo-purin-9-yl)methoxy-3-hydroxy-1-propanyl-L-valinate hydrochloride in crystalline form.
2. An antiviral pharmaceutical composition comprising the compound of claim 1 and a pharmaceutically acceptable excipient.

Thus, claim 1 covers the crystalline active ingredient of the approved product, and claim 2 the final pharmaceutical composition with excipients.

Claims 3-6 read as follows:

3. A method of treating an animal infected with a virus selected from herpes simplex virus and cytomegalovirus, comprising administering a therapeutically effective amount of the compound of claim 1 to the animal.
4. The method of claim 2 where the compound is administered orally.
5. The method of claim 3 where the herpes viral infection is a cytomegalovirus infection.

6. The method of claim 5 wherein the compound is administered orally.

Thus, claims 3-6 generically and specifically cover the administration of the approved product for the treatment of CMV infection.

In summary, as demonstrated above, claims 1and 2 read on the approved product and claims 3-6 on its approved indications of use.

(10) A Statement, Beginning on a New Page, of The Relevant Dates And Information Pursuant To 35 U.S.C. § 156(g) In Order To Enable The Secretary Of Health and Human Services or the Secretary of Agriculture, As Appropriate, To Determine the Applicable Regulatory Review Period as Follows (i): For A Patent Claiming A Human Drug Product, Antibiotic, or Human Biological Product, The Effective Date Of The Investigational New Drug (IND) Application And The IND Number; The Date On Which A New Drug Application (NDA) or a Product License Application (PLA) Was Initially Submitted And The NDA or PLA Number And The Date On which The NDA Was Approved or the Product License Issued

a)	Effective date of the investigational new drug application (IND) and IND number.	June 26, 1995 (Exhibit D) IND No. 48,106
b)	Date on which a New Drug Application (NDA) was initially submitted and NDA number:	September 28, 2000 (Exhibit E) NDA No. 21-304
c)	Date on which NDA was approved:	March 29, 2001 (Exhibit B)

(11) A Brief Description Beginning On A New Page Of The Significant Activities Undertaken By The Marketing Applicant During The Applicable Regulatory Review Period With Respect To The Approved Product And The Significant Dates Applicable To Such Activities

A chronology of significant activities undertaken by applicant during the regulatory review period with respect to the approved product is annexed as Exhibit F. This Exhibit specifically is directed to the communications between applicant and the FDA. The Exhibit provides the nature of each correspondence with the FDA, including a brief summary of its subject matter, and the date of the correspondence. For convenience, the chronology is divided into two sections: "Correspondence Log - Testing Phase" and "Correspondence Log - Application Phase."

If necessary, applicant reserves the right to supplement its chronology in Exhibit F with materials from which it was derived and other evidence related to applicant's conduct in obtaining the approval of Valcyte™. *See, e.g.,* 21 C.F.R. § 60.32.

(12) A Statement Beginning On A New Page That In The Opinion Of The Applicant The Patent Is Eligible For The Extension And A Statement As To The Length Of The Extension Claimed, Including How The Length Of Extension Was Determined

Eligibility

Under the law and in the opinion of Applicant, U.S. Patent No. 6,083,953 is eligible for an extension under 35 U.S.C. § 156.

In particular, 35 U.S.C. § 156(a) in its relevant parts, provides that the term of a patent shall be extended if the following requirements are satisfied: (1) the patent claims a product, a method of using a product or a method of manufacturing a product; (2) the term of the patent has not expired before an application for extension is submitted; (3) the term of the patent has never been extended; (4) an application for extension is submitted by the owner of record of the patent or its agent and in accordance with 35 U.S.C. § 156(d); (5) the product has been subject to a regulatory review period as defined in 35 U.S.C. § 156(a) before its commercial marketing or use; and (6) the permission for the commercial marketing or use of the product after the regulatory review period is the first permitted commercial marketing or use of the product under the provision of law under which such regulatory review period occurred.

These requirements are met as follows:

1. U.S. Patent No. 6,083,953 claims a product, and a method of using a product.
2. The term of U.S. Patent No. 6,083,953 presently will expire on July 28, 2014 and thus, the patent has not expired before submission of this Application.

3. The term of U.S. Patent No. 6,083,953 has never been extended under 35 U.S.C. § 156.

4. This Application is submitted by SYNTEX, the owner of record of U.S. Patent No. 6,083,953. This Application is submitted in accordance with 35 U.S.C. § 156(d) and 37 C.F.R. § 1.740 within the sixty (60) day period beginning on April 30, 1998 and ending on June 28, 1998. The product received permission for marketing or use under FD&C Act. This Application contains the information required under 35 U.S.C. § 156(d) and 37 C.F.R. § 1.740.

5. The product was subject to a regulatory review period under Sections 505 of the FD&C Act before its commercial marketing or use, as evidenced by the chronology (Exhibit F) and the Letter of Approval from the FDA, dated March 29, 2001(Exhibit B).

6. The permission for the commercial marketing or use of the approved product after the regulatory review period is the first permitted commercial marketing or use of a product having valganciclovir hydrochloride in any form as its active ingredient, under the provisions of the FD&C Act under which such regulatory review period occurred. This is confirmed by the absence of any approved drug application for the active ingredient (valganciclovir hydrochloride) of the approved product (Valcyte™) in any form prior to March 29, 2001.

Accordingly, U.S. Patent No. 6,083,953 satisfies the requirements for an extension under 35 U.S.C. § 156.

Length

In the opinion of Applicant, the term of U.S. patent No. 6,083,953 should be extended for 226 days from July 28, 2014 to and including March 11, 2015.

This extension was determined on the following basis:

Testing Phase (37 C.F.R. § 1.775(c) (1))

For the approved product, that portion of the regulatory review period as defined in 35 U.S.C. 156 (g) (1) (B) (i) ("Testing Phase") commenced on June 26, 1995 and ended on September 28, 2000, which is 1,922 days.

Application Phase (37 C.F.R. § 1.775(c) (2))

For the approved product, that portion of the regulatory review period as defined under 35 U.S.C. 156 (g) (1) (B) (ii) ("Application Phase") commenced on September 28, 2000 and ended on March 29, 2001, which is 183 days.

Regulatory Review Period (37 C.F.R. § 1.775(c))

As defined in 35 U.S.C. 156 (g) (1) (B), the regulatory review period is the sum of the Testing Phase and the Application Phase, which is a total of 2,105 days.

Reduction for Review Prior to the Issue of The Patent (37 C.F.R. § 1.775 (d) (1) (i))

The applicable regulatory review period is reduced by that period of review occurring before and on the date the patent issued.

U.S. Patent No. 6,083,953 (Exhibit C) issued July 4, 2000 and the effective date of the IND was June 26, 1995. Accordingly, a reduction of 1,836 days, all occurring in the Testing Phase, is applicable for the review period prior to the issue of the patent, leaving a revised Testing Phase of 86 days and a revised regulatory review period of 269 days.

Due Diligence Reduction to Regulatory Review Period (37 C.F.R. § 1.775 (d) (1) (ii))

Under 35 U.S.C. § 156(c) (1), the Testing Phase and Application Phase of the regulatory review period are reduced by the period during which the applicant for the patent extension, in the regulatory review period, did not act with due diligence. In the opinion of the Applicant and illustrated by the chronology in Exhibit F, Applicant acted with due diligence during both periods of time. Thus, there is no reduction in the regulatory review period because of lack of due diligence.

One-Half Testing Phase Reduction (37 C.F.R. § 1.775 (d) (1) (iii))

Under 35 U.S.C. § 156(c) (2), the regulatory review period is reduced by one-half of the remaining 86 day Testing Phase. This is 43 days. Thus, the remaining 269 day regulatory review period is further reduced by 43 days, leaving a final revised regulatory review period of 226 days.

Fourteen Year Cap (37 C.F.R. § 1.775 (d) (2) - (4)

Under 35 U.S.C. § 156(c) (3), should the period of time remaining in the term of the patent after the date of approval when added to the period of extension exceeds fourteen (14) years, the period of extension is reduced so that the total of both such periods does not exceed fourteen (14)

years. In applying section 156(c) (3), the final revised regulatory review period as calculated above (226 days) is added onto the end of the original term of the patent, July 28, 2014, resulting in a date of March 11, 2015. Alternatively, fourteen (14) years is added to the NDA approval date (March 29, 2001) resulting in a date of March 29, 2015. The earlier of the above two dates, March 11, 2015 is thus selected.

Two and Five Year Extension Limits (37 C.F.R. § 1.775 (d) (5) & (6)

A patent issued after September 24, 1984 is limited to a maximum extension of five years.

U.S. Patent No. 6,083,953 (Exhibit C) issued on July 4, 2000. Accordingly, the patent is eligible for an extension of up to five years.

As set forth above, the term of U.S. Patent No. 6,083,953 is eligible for an extension of 226 days to March 11, 2015.

(13) A Statement That Applicant Acknowledges A Duty To Disclose To The Commissioner Of Patents And Trademarks And The Secretary Of Health And Human Services Any Information Which Is Material To The Determination Of Entitlement To The Extension Sought

Applicant acknowledges a duty to disclose to the Commissioner of Patents and Trademarks ("the Commissioner") and the Secretary of Health and Human Services ("the Secretary") any information which is material to any determinations of entitlement to the extension sought in the Application.

(14) The Prescribed Fee for Receiving and Acting Upon the Application for Extension

Applicant encloses (in duplicate) a transmittal letter requesting the amount of $1120.00 be charged to Account No. 08-2525.

(15) The Name, Address and Telephone Number Of The Person to Whom Inquiries and Correspondence Relating To The Application For Patent Term Extension Are To Be Directed

Please address all correspondence to:

George W. Johnston
Hoffmann-La Roche Inc.
Patent Law Department
340 Kingsland Street
Nutley, New Jersey 07110

Please direct all telephone calls to:

Dennis P. Tramaloni
(973) 235-4475

(16) A Duplicate of These Application Papers, Certified As Such

A certified duplicate is enclosed.

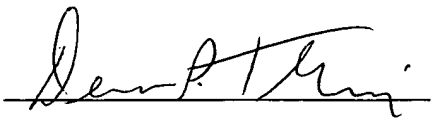
(17) An Oath or Declaration As Set Forth In Paragraph (b) of 37 C.F.R. § 1.740

Applicant attaches a declaration as set forth in 37 C.F.R. § 1.740(b), signed by an officer of SYNTEX, the owner of record of U.S. Patent No. 6,083,953, who is authorized to practice before the Patent and Trademark Office and who has general authority to act on SYNTEX's behalf in patent matters.

Request for Extension

Having included in this Application all of the requisite information under 35 U.S.C. § 156 and 37 C.F.R. § 1.740, Applicant requests (i) an extension of U.S. Patent No. 6,083,953 for 226 days from July 28, 2014 to and including March 11, 2015, by reason of its claims encompassing the approved product and its salts as a single entity or in combination with another active ingredient and (ii) certification that it is entitled to the rights derived from this patent as set forth in 35 U.S.C. § 156(b).

Respectfully submitted,

By: 

Dennis P. Tramaloni
Name (Print)

Senior Counsel & Managing Attorney
Title

Registration No. 28,542

May 23, 2001
Date

U.S. Patent No. 6,083,953
Issue Date: July 4, 2000

Certification

The undersigned certifies that this Application for Extension of Patent Term Under 35 U.S.C. § 156 including its exhibits is being submitted as duplicate originals.

By: _____
Dennis P. Tramaloni
Registration No. 28,542

Date: May 23, 2001

dpt:110529

PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re United States Patent 6,083,953

Attn: Box Patent Ext.

Inventors: John J. Nestor et al.

Issue Date: July 4, 2000

For: 2-(2-AMINO-1,6-DIHYDRO-6-OXO-PURIN-9-YL) METHOXY-1,3- PROPAPNEDIOL DERIVATIVE

DECLARATION AND POWER OF ATTORNEY FOR APPLICATION FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. §156

Palo Alto, California 94304
May 21, 2001

Commissioner for Patents
Washington, D.C. 20231
Attn: Box Patent Ext.

S i r:

I, Rohan Peries, a Vice President of Syntex (U.S.A.) LLC ("SYNTEX"), which submits the attached Application for Extension of Patent Term Under 35 U.S.C. § 156, of the same date as this Declaration, declare that:

(1) SYNTEX is the owner of record of U.S. Patent No. 6,083,953 and I am authorized to obligate SYNTEX;

(2) I am a patent attorney authorized to practice before the Patent and Trademark Office and have general authority from SYNTEX to act on its behalf in patent matters;

(3) I have reviewed and understand the contents of the Application being submitted for extension of the term of U.S. Patent No. 6,083,953 pursuant to 35 U.S.C. § 156 and 37 C.F.R. §1.710 et seq;

(4) I believe this patent is subject to extension under 35 U.S.C. § 156 and 37 C.F.R. §1.710;

(5) I believe an extension of the length claimed is justified under 35 U.S.C. § 156 and the applicable regulations; and

(6) I believe the patent for which the extension is being sought meets the conditions for extension of the term of a patent as set forth in 35 U.S.C. § 156, and more particularly, in 37 C.F.R. §1.720.

I hereby appoint the following attorneys as agents for SYNTEX under 35 U.S.C. § 156 with the authority to sign, submit and prosecute this Application and transact all business in the Patent and Trademark Office and with the Secretary of Health and Human Services connected therewith: George W. Johnston (Reg. No. 28090), William H. Epstein (Reg. No. 20008), Dennis P. Tramaloni (Reg. No. 28542) and Patricia S. Rocha-Tramaloni (Reg. No. 31054).

Send correspondence to:

George W. Johnston
Hoffmann-La Roche Inc.
Patent Law Department
340 Kingsland Street
Nutley, New Jersey 07110

Direct Telephone Calls to:

Dennis P. Tramaloni
(973) 235-4475

I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of this patent extension application or any extension of U.S. Patent No. 6,083,953.

Respectfully submitted,
SYNTEX (U.S.A.) LLC

By: _____
Rohan Peries
Vice President

Date: May 21, 2001

110576

In re United States Patent No. 6,083,953
Issued July 4, 2000

EXHIBITS TO

APPLICATION FOR EXTENSION OF PATENT TERM

UNDER 35 U.S.C. § 156

Roche

VALCYTE™
(valganciclovir hydrochloride tablets)

WARNING

THE CLINICAL TOXICITY OF VALCYTE, WHICH IS METABOLIZED TO GANCICLOVIR, INCLUDES GRANULOCYTOPENIA, ANEMIA AND THROMBOCYTOPENIA. IN ANIMAL STUDIES GANCICLOVIR WAS CARCINOGENIC, TERATOGENIC AND CAUSED ASPERMATOGENESIS.

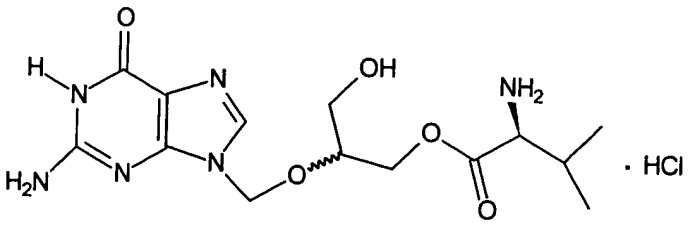
DESCRIPTION

Valcyte (valganciclovir HCl tablets) contains valganciclovir hydrochloride (valganciclovir HCl), a hydrochloride salt of the L-valyl ester of ganciclovir that exists as a mixture of two diastereomers. Ganciclovir is a synthetic guanine derivative active against cytomegalovirus (CMV).

Valganciclovir is available as a 450 mg tablet for oral administration. Each tablet contains 496.3 mg of valganciclovir HCl (corresponding to 450 mg of valganciclovir), and the inactive ingredients microcrystalline cellulose, povidone K-30, crospovidone, and stearic acid. The film-coat applied to the tablets contains Opadry Pink®.

Valganciclovir HCl is a white to off-white crystalline powder with a molecular formula of $C_{14}H_{22}N_6O_5 \cdot HCl$ and a molecular weight of 390.83. The chemical name for valganciclovir HCl is L-Valine, 2-[(2-amino-1,6-dihydro-6-oxo-9H-purin-9-yl)methoxy]-3-hydroxypropyl ester, monohydrochloride. Valganciclovir HCl is a polar hydrophilic compound with a solubility of 70 mg/mL in water at 25°C at a pH of 7.0 and an n-octanol/water partition coefficient of 0.0095 at pH 7.0. The pKa for valganciclovir is 7.6.

The chemical structure of valganciclovir HCl is:



All doses in this insert are specified in terms of valganciclovir.

VIROLOGY

Mechanism of Action

Valcyte™ (valganciclovir HCl tablets)

Valganciclovir is an L-valyl ester (prodrug) of ganciclovir that exists as a mixture of two diastereomers. After oral administration, both diastereomers are rapidly converted to ganciclovir by intestinal and hepatic esterases. Ganciclovir is a synthetic analogue of 2'-deoxyguanosine, which inhibits replication of human cytomegalovirus in vitro and in vivo.

In CMV-infected cells ganciclovir is initially phosphorylated to ganciclovir monophosphate by the viral protein kinase, pUL97. Further phosphorylation occurs by cellular kinases to produce ganciclovir triphosphate, which is then slowly metabolized intracellularly (half-life 18 hours). As the phosphorylation is largely dependent on the viral kinase, phosphorylation of ganciclovir occurs preferentially in virus-infected cells. The virustatic activity of ganciclovir is due to inhibition of viral DNA synthesis by ganciclovir triphosphate.

Antiviral Activity

The quantitative relationship between the in vitro susceptibility of human herpesviruses to antivirals and clinical response to antiviral therapy has not been established, and virus sensitivity testing has not been standardized. Sensitivity test results, expressed as the concentration of drug required to inhibit the growth of virus in cell culture by 50% (IC_{50}), vary greatly depending upon a number of factors. Thus the IC_{50} of ganciclovir that inhibits human CMV replication in vitro (laboratory and clinical isolates) has ranged from 0.02 to 5.75 μg/mL (0.08 to 22.94 μM). Ganciclovir inhibits mammalian cell proliferation (CIC_{50}) in vitro at higher concentrations ranging from 10.21 to >250 μg/mL (40 to >1000 μM). Bone marrow-derived colony-forming cells are more sensitive (CIC_{50} = 0.69 to 3.06 μg/mL: 2.7 to 12 μM).

Viral Resistance

Viruses resistant to ganciclovir can arise after prolonged treatment with valganciclovir by selection of mutations in either the viral protein kinase gene (UL97) responsible for ganciclovir monophosphorylation and/or in the viral polymerase gene (UL54). Virus with mutations in the UL97 gene is resistant to ganciclovir alone, whereas virus with mutations in the UL54 gene may show cross-resistance to other antivirals with a similar mechanism of action.

The current working definition of CMV resistance to ganciclovir in in vitro assays is $IC_{50} \geq 1.5$ μg/mL (≥ 6.0 μM). CMV resistance to ganciclovir has been observed in individuals with AIDS and CMV retinitis who have never received ganciclovir therapy. Viral resistance has also been observed in patients receiving prolonged treatment for CMV retinitis with ganciclovir. The possibility of viral resistance should be considered in patients who show poor clinical response or experience persistent viral excretion during therapy.

CLINICAL PHARMACOLOGY

Pharmacokinetics

Valcyte™ (valganciclovir HCl tablets)

BECAUSE THE MAJOR ELIMINATION PATHWAY FOR GANCICLOVIR IS RENAL, DOSAGE REDUCTIONS ACCORDING TO CREATININE CLEARANCE ARE REQUIRED FOR VALCYTE TABLETS. FOR DOSING INSTRUCTIONS IN PATIENTS WITH RENAL IMPAIRMENT, REFER TO DOSAGE AND ADMINISTRATION.

The ganciclovir pharmacokinetic measures following administration of 900 mg valganciclovir and 5 mg/kg intravenous ganciclovir and 1000 mg three times daily oral ganciclovir are summarized in Table 1.

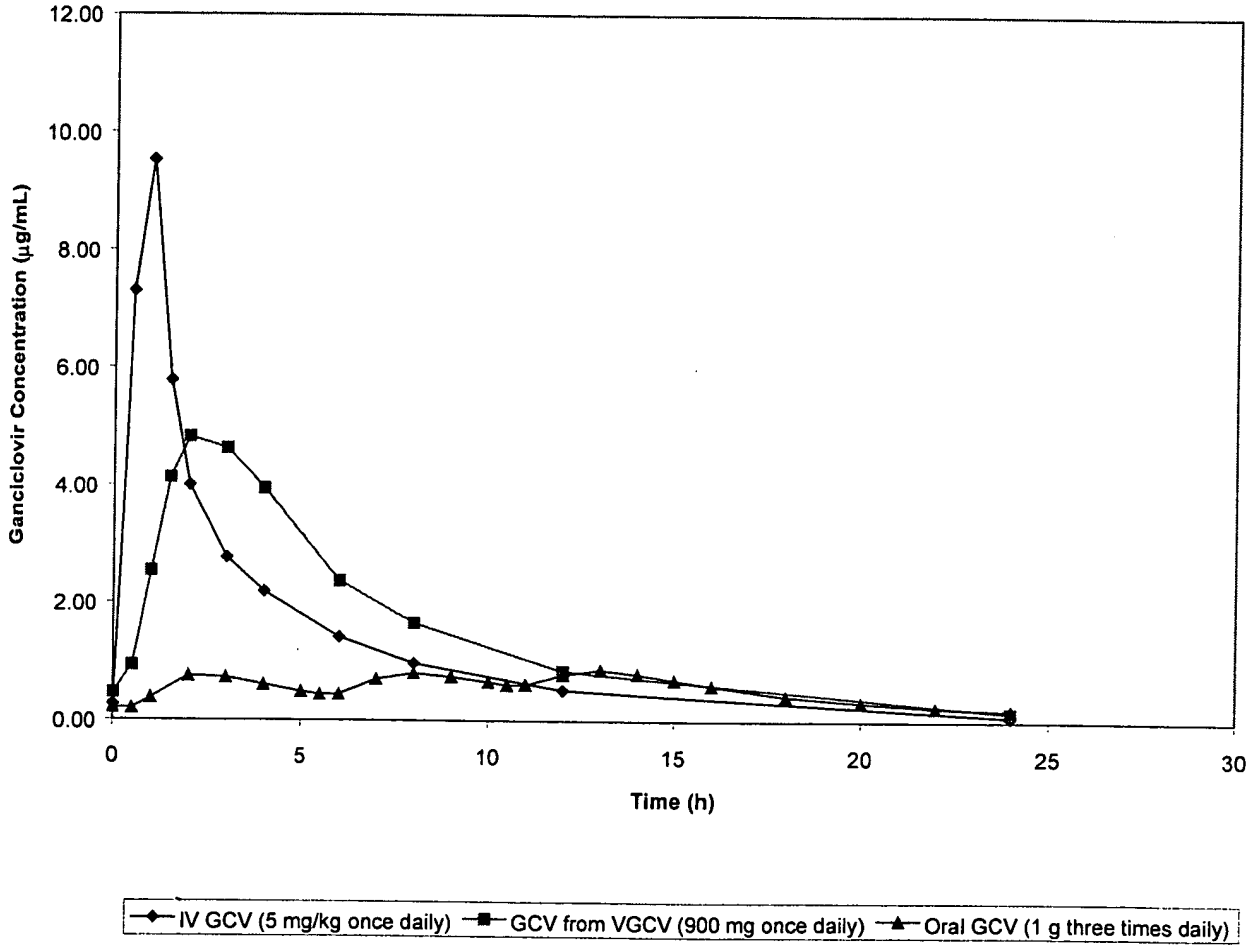
Table 1. Mean Ganciclovir Pharmacokinetic* Measures in Healthy Volunteers and HIV-positive/CMV-positive Adults at Maintenance Dosage

Formulation	Valcyte Tablets	Cytovene®-IV	Cytovene®
Dosage	900 mg once daily with food	5 mg/kg once daily	1000 mg three times daily with food
$AUC_{0\text{-}24\ hr}$ (μg·h/mL)	29.1 ± 9.7 (3 studies, n=57)	26.5 ± 5.9 (4 studies, n=68)	Range of means 12.3 to 19.2 (6 studies, n=94)
C_{max} (μg/mL)	5.61 ± 1.52 (3 studies, n=58)	9.46 ± 2.02 (4 studies, n=68)	Range of means 0.955 to 1.40 (6 studies, n=94)
Absolute oral bioavailability (%)	59.4 ± 6.1 (2 studies, n=32)	Not Applicable	Range of means 6.22 ± 1.29 to 8.53 ± 1.53 (2 studies, n=32)
Elimination half-life (hr)	4.08 ± 0.76 (4 studies, n=73)	3.81 ± 0.71 (4 studies, n=69)	Range of means 3.86 to 5.03 (4 studies, n=61)
Renal clearance (mL/min/kg)	3.21 ± 0.75 (1 study, n=20)	2.99 ± 0.67 (1 study, n=16)	Range of means 2.67 to 3.98 (3 studies, n=30)

* Data were obtained from single and multiple dose studies in healthy volunteers, HIV-positive patients, and HIV-positive/CMV-positive patients with and without retinitis. Patients with CMV retinitis tended to have higher ganciclovir plasma concentrations than patients without CMV retinitis.

The area under the plasma concentration-time curve (AUC) for ganciclovir administered as Valcyte tablets is comparable to the ganciclovir AUC for intravenous ganciclovir. Ganciclovir C_{max} following valganciclovir administration is 40% lower than following intravenous ganciclovir administration. During maintenance dosing, ganciclovir $AUC_{0\text{-}24\ hr}$ and C_{max} following oral ganciclovir administration (1000 mg three times daily) are lower relative to valganciclovir and intravenous ganciclovir. The ganciclovir C_{min} following intravenous ganciclovir and valganciclovir administration are less than the ganciclovir C_{min} following oral ganciclovir administration. The clinical significance of the differences in ganciclovir pharmacokinetics for these three ganciclovir delivery systems is unknown.

Figure 1. Ganciclovir Plasma Concentration Time Profiles in HIV-positive/CMV-positive Patients*



* Plasma concentration-time profiles for ganciclovir (GCV) from valganciclovir (VGCV) and intravenous ganciclovir were obtained from a multiple dose study (WV15376 n=21 and n=18, respectively) in HIV-positive/CMV-positive patients with CMV retinitis. The plasma concentration-time profile for oral ganciclovir was obtained from a multiple dose study (GAN2230 n=24) in HIV-positive/CMV-positive patients without CMV retinitis.

Valcyte™ (valganciclovir HCl tablets)

Absorption

Valganciclovir, a prodrug of ganciclovir, is well absorbed from the gastrointestinal tract and rapidly metabolized in the intestinal wall and liver to ganciclovir. The absolute bioavailability of ganciclovir from Valcyte tablets following administration with food was approximately 60% (3 studies, n=18; n=16; n=28). Ganciclovir median T_{max} following administration of 450 mg to 2625 mg valganciclovir tablets ranged from 1 to 3 hours. Dose proportionality with respect to ganciclovir AUC following administration of valganciclovir tablets was demonstrated only under fed conditions. Systemic exposure to the prodrug, valganciclovir, is transient and low, and the AUC_{24} and C_{max} values are approximately 1% and 3% of those of ganciclovir, respectively.

Food Effects

When valganciclovir tablets were administered with a high fat meal containing approximately 600 total calories (31.1 g fat, 51.6 g carbohydrates, and 22.2 g protein) at a dose of 875 mg once daily to 16 HIV-positive subjects, the steady-state ganciclovir AUC increased by 30% (95% CI 12-51%), and the C_{max} increased by 14% (95% CI -5-36%), without any prolongation in time to peak plasma concentrations (T_{max}). Valcyte tablets should be administered with food (see DOSAGE AND ADMINISTRATION).

Distribution

Due to the rapid conversion of valganciclovir to ganciclovir, plasma protein binding of valganciclovir was not determined. Plasma protein binding of ganciclovir is 1% to 2% over concentrations of 0.5 and 51 μg/ml. When ganciclovir was administered intravenously, the steady state volume of distribution of ganciclovir was 0.703 ± 0.134 L/kg (n=69).

After administration of valganciclovir tablets, no correlation was observed between ganciclovir AUC and reciprocal weight; oral dosing of valganciclovir tablets according to weight is not required.

Metabolism

Valganciclovir is rapidly hydrolyzed to ganciclovir; no other metabolites have been detected. No metabolite of orally-administered radiolabeled ganciclovir (1000 mg single dose) accounted for more than 1% to 2% of the radioactivity recovered in the feces or urine.

Elimination

The major route of elimination of valganciclovir is by renal excretion as ganciclovir through glomerular filtration and active tubular secretion. Systemic clearance of intravenously administered ganciclovir was 3.07 ± 0.64 mL/min/kg (n=68) while renal clearance was 2.99± 0.67 mL/min/kg (n=16).

The terminal half-life ($t_{½}$) of ganciclovir following oral administration of valganciclovir tablets to either healthy or HIV-positive/CMV-positive subjects was 4.08 ± 0.76 hours (n=73), and that following administration of intravenous ganciclovir was 3.81 ± 0.71 hours (n=69).

Special Populations

Renal Impairment

The pharmacokinetics of ganciclovir from a single oral dose of 900 mg Valcyte tablets were evaluated in 24 otherwise healthy individuals with renal impairment.

Table 2. Pharmacokinetics of Ganciclovir From a Single Oral Dose of 900 mg Valcyte Tablets

Estimated Creatinine Clearance (mL/min)	N	Apparent Clearance (mL/min) Mean ± SD	AUC_{last} (μg·h/mL) Mean ± SD	Half-life (hours) Mean ± SD
51-70	6	249 ± 99	49.5 ± 22.4	4.85 ± 1.4
21-50	6	136 ± 64	91.9 ± 43.9	10.2 ± 4.4
11-20	6	45 ± 11	223 ± 46	21.8 ± 5.2
≤10	6	12.8 ± 8	366 ± 66	67.5 ± 34

Decreased renal function results in decreased clearance of ganciclovir from valganciclovir, and a corresponding increase in terminal half-life. Therefore, dosage adjustment is required for patients with impaired renal function (see PRECAUTIONS: General).

Hemodialysis

Hemodialysis reduces plasma concentrations of ganciclovir by about 50% following valganciclovir administration. Patients receiving hemodialysis (CrCl <10 ml/min) cannot use Valcyte tablets because the daily dose of Valcyte tablets required for these patients is less than 450 mg (see PRECAUTIONS: General and DOSAGE AND ADMINISTRATION: Hemodialysis Patients).

Liver Transplant Patients

In liver transplant patients, the ganciclovir $AUC_{0\text{-}24\ hr}$ achieved with 900 mg valganciclovir was 41.7 ± 9.9 μg·h/mL (n=28) and the $AUC_{0\text{-}24\ hr}$ achieved with the approved dosage of 5 mg/kg intravenous ganciclovir was 48.2 ± 17.3 μg·h/mL (n=27).

Race/Ethnicity and Gender

Insufficient data are available to demonstrate any effect of race or gender on the pharmacokinetics of valganciclovir.

Pediatrics

Valcyte tablets have not been studied in pediatric patients; the pharmacokinetic characteristics of Valcyte tablets in these patients have not been established (see PRECAUTIONS: Pediatric Use).

Geriatrics

No studies of Valcyte tablets have been conducted in adults older than 65 years of age (see PRECAUTIONS: Geriatric Use).

INDICATIONS AND USAGE

Valcyte tablets are indicated for the treatment of cytomegalovirus (CMV) retinitis in patients with acquired immunodeficiency syndrome (AIDS) (see CLINICAL TRIALS).

CLINICAL TRIALS

Induction Therapy of CMV Retinitis

Study WV15376

In a randomized, open-label controlled study, 160 patients with AIDS and newly diagnosed CMV retinitis were randomized to receive treatment with either Valcyte tablets (900 mg twice daily for 21 days, then 900 mg once daily for 7 days) or with intravenous ganciclovir solution (5 mg/kg twice daily for 21 days, then 5 mg/kg once daily for 7 days). Study participants were: male (91%), White (53%), Hispanic (31%), and Black (11%). The median age was 39 years, the median baseline HIV-1 RNA was 4.9 $\log_{10}$, and the median CD4 cell count was 23 cells/mm^3. A determination of CMV retinitis progression by the masked review of retinal photographs taken at baseline and week 4 was the primary outcome measurement of the three week induction therapy. Table 3 provides the outcomes at four weeks.

Table 3. Week 4 Masked Review of Retinal Photographs in Study WV15376

	Cytovene-IV	Valcyte
Determination of CMV retinitis progression at Week 4	N=80	N=80
Progressor	7	7
Non-progressor	63	64
Death	2	1
Discontinuations due to Adverse Events	1	2
Failed to return	1	1
CMV not confirmed at baseline or no interpretable baseline photos	6	5

Maintenance Therapy of CMV Retinitis

No comparative clinical data are available on the efficacy of Valcyte for the maintenance therapy of CMV retinitis because all patients in study WV15376 received open-label Valcyte after week 4. However, the AUC for ganciclovir is similar following administration of 900 mg valganciclovir once daily and 5 mg/kg intravenous ganciclovir once daily. Although the ganciclovir C_{max} is lower following valganciclovir administration compared to intravenous ganciclovir, it is higher than the C_{max} obtained following oral ganciclovir administration (see Figure 1 in CLINICAL PHARMACOLOGY). Therefore, use of valganciclovir as maintenance therapy is supported by a plasma concentration-time profile similar to that of two approved products for maintenance therapy of CMV retinitis.

CONTRAINDICATIONS

Valcyte tablets are contraindicated in patients with hypersensitivity to valganciclovir or ganciclovir.

WARNINGS

THE CLINICAL TOXICITY OF VALCYTE , WHICH IS METABOLIZED TO GANCICLOVIR, INCLUDES GRANULOCYTOPENIA, ANEMIA AND THROMBOCYTOPENIA. IN ANIMAL STUDIES GANCICLOVIR WAS CARCINOGENIC, TERATOGENIC AND CAUSED ASPERMATOGENESIS.

Hematologic

Valcyte tablets should not be administered if the absolute neutrophil count is less than 500 cells/μL, the platelet count is less than 25,000/μL, or the hemoglobin is less than 8 g/dL.

Severe leukopenia, neutropenia, anemia, thrombocytopenia, pancytopenia, bone marrow depression and aplastic anemia have been observed in patients treated with Valcyte tablets (and ganciclovir) (see PRECAUTIONS: Laboratory Testing and ADVERSE EVENTS).

Valcyte tablets should, therefore, be used with caution in patients with pre-existing cytopenias, or who have received or who are receiving myelosuppressive drugs or irradiation. Cytopenia may occur at any time during treatment and may increase with continued dosing. Cell counts usually begin to recover within 3 to 7 days of discontinuing drug.

Impairment of Fertility

Animal data indicate that administration of ganciclovir causes inhibition of spermatogenesis and subsequent infertility. These effects were reversible at lower doses and irreversible at higher doses (see PRECAUTIONS: Carcinogenesis, Mutagenesis and Impairment of Fertility). It is considered probable that in humans, valganciclovir at the recommended doses may cause temporary or permanent inhibition of spermatogenesis. Animal data also indicate that suppression of fertility in females may occur.

Teratogenesis, Carcinogenesis and Mutagenesis

Because of the mutagenic and teratogenic potential of ganciclovir, women of childbearing potential should be advised to use effective contraception during treatment. Similarly, men should be advised to practice barrier contraception during, and for at least 90 days following, treatment with Valcyte tablets (see PRECAUTIONS: Carcinogenesis, Mutagenesis and Pregnancy: Category C).

In animal studies, ganciclovir was found to be mutagenic and carcinogenic. Valganciclovir should, therefore, be considered a potential teratogen and carcinogen in humans with the potential to cause birth defects and cancers (see DOSAGE AND ADMINISTRATION: Handling and Disposal).

PRECAUTIONS

General

Strict adherence to dosage recommendations is essential to avoid overdose.

The bioavailability of ganciclovir from Valcyte tablets is significantly higher than from ganciclovir capsules. Patients switching from ganciclovir capsules should be advised of the risk of overdosage if they take more than the prescribed number of Valcyte tablets. **Valcyte tablets cannot be substituted for Cytovene capsules on a one-to-one basis** (see OVERDOSAGE and DOSAGE AND ADMINISTRATION).

Since ganciclovir is excreted by the kidneys, normal clearance depends on adequate renal function. **IF RENAL FUNCTION IS IMPAIRED, DOSAGE ADJUSTMENTS ARE REQUIRED FOR VALCYTE TABLETS.** Such adjustments should be based on measured or estimated creatinine clearance values (see DOSAGE AND ADMINISTRATION: Renal Impairment).

For patients on hemodialysis (CrCl <10 mL/min) it is recommended that ganciclovir be used (in accordance with the dose-reduction algorithm cited in the Cytovene®-IV and Cytovene® Package Insert section on DOSAGE AND ADMINISTRATION: Renal Impairment) rather than Valcyte tablets (see DOSAGE AND ADMINISTRATION: Hemodialysis and CLINICAL PHARMACOLOGY: Special Populations: *Hemodialysis*).

Information for Patients (see Patient Package Insert)

Valcyte tablets cannot be substituted for ganciclovir capsules on a one-to-one basis. Patients switching from ganciclovir capsules should be advised of the risk of overdosage if they take more than the prescribed number of Valcyte tablets (see OVERDOSAGE and DOSAGE AND ADMINISTRATION).

Valcyte is changed to ganciclovir once it is absorbed into the body. All patients should be informed that the major toxicities of ganciclovir include granulocytopenia (neutropenia), anemia and thrombocytopenia and that dose modifications may be required, including discontinuation. The importance of close monitoring of blood counts while on therapy should be emphasized. Patients should be informed that ganciclovir has been associated with elevations in serum creatinine.

Patients should be instructed to take Valcyte tablets with food to maximize bioavailability.

Patients should be advised that ganciclovir has caused decreased sperm production in animals and may cause decreased fertility in humans. Women of childbearing potential should be advised that ganciclovir causes birth defects in animals and should not be used during pregnancy. Because of the potential for serious adverse events in nursing infants, mothers should be instructed not to breastfeed if they are receiving Valcyte tablets. Women of childbearing potential should be advised to use effective contraception during treatment with Valcyte tablets. Similarly, men should be advised to practice barrier contraception during and for at least 90 days following treatment with Valcyte tablets.

Although there is no information from human studies, patients should be advised that ganciclovir should be considered a potential carcinogen.

Convulsions, sedation, dizziness, ataxia and/or confusion have been reported with the use of Valcyte tablets and/or ganciclovir. If they occur, such effects may affect tasks requiring alertness including the patient's ability to drive and operate machinery.

Patients should be told that ganciclovir is not a cure for CMV retinitis, and that they may continue to experience progression of retinitis during or following treatment. Patients should be advised to have ophthalmologic follow-up examinations at a minimum of every 4 to 6 weeks while being treated with Valcyte tablets. Some patients will require more frequent follow-up.

Laboratory Testing

Due to the frequency of neutropenia, anemia and thrombocytopenia in patients receiving Valcyte tablets (see ADVERSE EVENTS), it is recommended that complete blood counts and platelet counts

be performed frequently, especially in patients in whom ganciclovir or other nucleoside analogues have previously resulted in leukopenia, or in whom neutrophil counts are less than 1000 cells/μL at the beginning of treatment. Increased monitoring for cytopenias may be warranted if therapy with oral ganciclovir is changed to oral valganciclovir, because of increased plasma concentrations of ganciclovir after valganciclovir administration (see CLINICAL PHARMACOLOGY).

Increased serum creatinine levels have been observed in trials evaluating Valcyte tablets. Patients should have serum creatinine or creatinine clearance values monitored carefully to allow for dosage adjustments in renally impaired patients (see DOSAGE AND ADMINISTRATION: Renal Impairment). The mechanism of impairment of renal function is not known.

Drug Interactions

Drug Interaction Studies Conducted With Valganciclovir:

No in vivo drug-drug interaction studies were conducted with valganciclovir. However, because valganciclovir is rapidly and extensively converted to ganciclovir, interactions associated with ganciclovir will be expected for Valcyte tablets.

Drug Interaction Studies Conducted With Ganciclovir:

Binding of ganciclovir to plasma proteins is only about 1% to 2%, and drug interactions involving binding site displacement are not anticipated.

Drug-drug interaction studies were conducted in patients with normal renal function. Patients with impaired renal function may have increased concentrations of ganciclovir and the coadministered drug following concomitant administration of Valcyte tablets and drugs excreted by the same pathway as ganciclovir. Therefore, these patients should be closely monitored for toxicity of ganciclovir and the coadministered drug.

Table 4. Results of Drug Interaction Studies with Ganciclovir: Effects of Co-administered Drug on Ganciclovir Plasma AUC and C_{max} Values

Co-administered Drug	Ganciclovir Dosage	n	Ganciclovir Pharmacokinetic (PK) Parameter	Clinical Comment
Zidovudine 100 mg every 4 hours	1000 mg every 8 hours	12	AUC ↓ 17 ± 25% (range: -52% to 23%)	Zidovudine and Valcyte each have the potential to cause neutropenia and anemia. Some patients may not tolerate concomitant therapy at full dosage.
Didanosine 200 mg every 12 hours administered 2 hours before ganciclovir	1000 mg every 8 hours	12	AUC ↓ 21 ± 17% (range: -44% to 5%)	Effect not likely to be clinically significant.
Didanosine 200 mg every 12 hours simultaneously administered with ganciclovir	1000 mg every 8 hours	12	No effect on ganciclovir PK parameters observed	No effect expected.
	IV ganciclovir 5 mg/kg twice daily	11	No effect on ganciclovir PK parameters observed	No effect expected.
	IV ganciclovir 5 mg/kg once daily	11	No effect on ganciclovir PK parameters observed	No effect expected.
Probenecid 500 mg every 6 hours	1000 mg every 8 hours	10	AUC ↑ 53 ± 91% (range: -14% to 299%) Ganciclovir renal clearance ↓ 22 ± 20% (Range: -54% to -4%)	Patients taking probenecid and Valcyte should be monitored for evidence of ganciclovir toxicity.
Zalcitabine 0.75 mg every 8 hours administered 2 hours before ganciclovir	1000 mg every 8 hours	10	AUC ↑ 13%	Effect not likely to be clinically significant.
Trimethoprim 200 mg once daily	1000 mg every 8 hours	12	Ganciclovir renal clearance ↓ 16.3% Half-life ↑ 15%	Effect not likely to be clinically significant.
Mycophenolate Mofetil 1.5 g single dose	IV ganciclovir 5 mg/kg single dose	12	No effect on ganciclovir PK parameters observed (patients with normal renal function)	Patients with renal impairment should be monitored carefully as levels of metabolites of both drugs may increase.

Table 5. Results of Drug Interaction Studies with ganciclovir: Effects of ganciclovir on Plasma AUC and C_{max} Values of Co-administered Drug

Co-administered Drug	Ganciclovir Dosage	n	Co-administered Drug Pharmacokinetic (PK) Parameter	Clinical Comment
Zidovudine 100 mg every 4 hours	1000 mg every 8 hours	12	AUC_{0-4} ↑ 19 ± 27% (range: -11% to 74%)	Zidovudine and Valcyte each have the potential to cause neutropenia and anemia. Some patients may not tolerate concomitant therapy at full dosage.
Didanosine 200 mg every 12 hours when administered 2 hours prior to or concurrent with ganciclovir	1000 mg every 8 hours	12	AUC_{0-12} ↑ 111 ± 114% (range: 10% to 493%)	Patients should be closely monitored for didanosine toxicity.
Didanosine 200 mg every 12 hours	IV ganciclovir 5 mg/kg twice daily	11	AUC_{0-12} ↑ 70 ± 40% (range: 3% to 121%) C_{max} ↑ 49 ± 48% (range: -28% to 125%)	Patients should be closely monitored for didanosine toxicity.
Didanosine 200 mg every 12 hours	IV ganciclovir 5 mg/kg once daily	11	AUC_{0-12} ↑ 50 ± 26% (range: 22% to 110%) C_{max} ↑ 36 ± 36% (range: -27% to 94%)	Patients should be closely monitored for didanosine toxicity.
Zalcitabine 0.75 mg every 8 hours administered 2 hours before ganciclovir	1000 mg every 8 hours	10	No clinically relevant PK parameter changes	No effect expected.
Trimethoprim 200 mg once daily	1000 mg every 8 hours	12	Increase in C_{min}	Effect not likely to be clinically significant.
Mycophenolate Mofetil 1.5 g single dose	IV ganciclovir 5 mg/kg single dose	12	No PK interaction observed (patients with normal renal function)	Patients with renal impairment should be monitored carefully as levels of metabolites of both drugs may increase.

Carcinogenesis, Mutagenesis and Impairment of Fertility‡

No long-term carcinogenicity studies have been conducted with valganciclovir. However, upon oral administration, valganciclovir is rapidly and extensively converted to ganciclovir. Therefore, like ganciclovir, valganciclovir is a potential carcinogen.

Ganciclovir was carcinogenic in the mouse at oral doses of 20 and 1000 mg/kg/day (approximately 0.1x and 1.4x, respectively, the mean drug exposure in humans following the recommended intravenous dose of 5 mg/kg, based on area under the plasma concentration curve [AUC] comparisons). At the dose of 1000 mg/kg/day there was a significant increase in the incidence of tumors of the preputial gland in males, forestomach (nonglandular mucosa) in males and females, and reproductive tissues (ovaries, uterus, mammary gland, clitoral gland and vagina) and liver in females. At the dose of 20 mg/kg/day, a slightly increased incidence of tumors was noted in the preputial and harderian glands in males, forestomach in males and females, and liver in females. No carcinogenic effect was observed in mice administered ganciclovir at 1 mg/kg/day (estimated as 0.01x the human dose based on AUC comparison). Ganciclovir should be considered a potential carcinogen in humans.

Valganciclovir increases mutations in mouse lymphoma cells. In the mouse micronucleus assay, valganciclovir was clastogenic at a dose of 1500 mg/kg (60x human mean exposure for ganciclovir based upon AUC). Valganciclovir was not mutagenic in the Ames Salmonella assay. Ganciclovir increased mutations in mouse lymphoma cells and DNA damage in human lymphocytes in vitro. In the mouse micronucleus assay, ganciclovir was clastogenic at doses of 150 and 500 mg/kg (IV) (2.8 to 10x human exposure based on AUC) but not 50 mg/kg (exposure approximately comparable to the human based on AUC). Ganciclovir was not mutagenic in the Ames Salmonella assay.

Valganciclovir is converted to ganciclovir and therefore is expected to have similar reproductive toxicity effects as ganciclovir (see WARNINGS: Impairment of Fertility). Ganciclovir caused decreased mating behavior, decreased fertility, and an increased incidence of embryolethality in female mice following intravenous doses of 90 mg/kg/day (approximately 1.7x the mean drug exposure in humans following the dose of 5 mg/kg, based on AUC comparisons). Ganciclovir caused decreased fertility in male mice and hypospermatogenesis in mice and dogs following daily oral or intravenous administration of doses ranging from 0.2 to 10 mg/kg. Systemic drug exposure (AUC) at the lowest dose showing toxicity in each species ranged from 0.03 to 0.1x the AUC of the recommended human intravenous dose. Valganciclovir caused similar effects on spermatogenesis in mice, rats, and dogs. It is considered likely that ganciclovir (and valganciclovir) could cause inhibition of human spermatogenesis.

Pregnancy

Category C‡

Valganciclovir is converted to ganciclovir and therefore is expected to have reproductive toxicity effects similar to ganciclovir. Ganciclovir has been shown to be embryotoxic in rabbits and mice following intravenous administration, and teratogenic in rabbits. Fetal resorptions were present in at least 85% of rabbits and mice administered 60 mg/kg/day and 108 mg/kg/day (2x the human exposure

based on AUC comparisons), respectively. Effects observed in rabbits included: fetal growth retardation, embryolethality, teratogenicity and/or maternal toxicity. Teratogenic changes included cleft palate, anophthalmia/microphthalmia, aplastic organs (kidney and pancreas), hydrocephaly and brachygnathia. In mice, effects observed were maternal/fetal toxicity and embryolethality.

Daily intravenous doses of 90 mg/kg administered to female mice prior to mating, during gestation, and during lactation caused hypoplasia of the testes and seminal vesicles in the month-old male offspring, as well as pathologic changes in the nonglandular region of the stomach (see Teratogenesis, Carcinogenesis and Mutagenesis). The drug exposure in mice as estimated by the AUC was approximately 1.7x the human AUC.

Data obtained using an ex vivo human placental model show that ganciclovir crosses the placenta and that simple diffusion is the most likely mechanism of transfer. The transfer was not saturable over a concentration range of 1 to 10 mg/mL and occurred by passive diffusion.

Valganciclovir may be teratogenic or embryotoxic at dose levels recommended for human use. There are no adequate and well-controlled studies in pregnant women. Valcyte tablets should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

‡ **Footnote:** All dose comparisons presented in the Carcinogenesis, Mutagenesis, Impairment of Fertility, and Pregnancy subsections are based on the human AUC following administration of a single 5 mg/kg infusion of intravenous ganciclovir.

Nursing Mothers

It is not known whether ganciclovir or valganciclovir is excreted in human milk. Because valganciclovir caused granulocytopenia, anemia and thrombocytopenia in clinical trials and ganciclovir was mutagenic and carcinogenic in animal studies, the possibility of serious adverse events from ganciclovir in nursing infants is possible (see WARNINGS). Because of potential for serious adverse events in nursing infants, **mothers should be instructed not to breastfeed if they are receiving Valcyte tablets.** In addition, the Centers for Disease Control and Prevention recommend that HIV-infected mothers not breastfeed their infants to avoid risking postnatal transmission of HIV.

Pediatric Use

Safety and effectiveness of Valcyte tablets in pediatric patients have not been established.

Geriatric Use

The pharmacokinetic characteristics of Valcyte in elderly patients have not been established. Since elderly individuals frequently have a reduced glomerular filtration rate, particular attention should be paid to assessing renal function before and during administration of Valcyte (see DOSAGE AND ADMINISTRATION).

Clinical studies of Valcyte did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. Valcyte is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection. In addition, renal function should be monitored and dosage adjustments should be made accordingly (see PRECAUTIONS: General, CLINICAL PHARMACOLOGY: Special Populations: *Renal Impairment*, and DOSAGE AND ADMINISTRATION: Renal Impairment).

ADVERSE EVENTS

Experience With Valcyte Tablets

Valganciclovir, a prodrug of ganciclovir, is rapidly converted to ganciclovir after oral administration. Adverse events known to be associated with ganciclovir usage can therefore be expected to occur with Valcyte tablets.

As shown in Table 6, the safety profiles of Valcyte tablets and intravenous ganciclovir during 28 days of randomized therapy (21 days induction dose and 7 days maintenance dose) in 158 patients were comparable, with the exception of catheter-related infection, which occurred with greater frequency in patients randomized to receive IV ganciclovir (see Table 6).

Table 6. Percentage of Selected Adverse Events Occurring During the Randomized Phase of Study WV15376

Adverse Event	Valganciclovir Arm N=79	Intravenous Ganciclovir Arm N=79
Diarrhea	16%	10%
Neutropenia	11%	13%
Nausea	8%	14%
Headache	9%	5%
Anemia	8%	8%
Catheter-related infection	3%	11%

Tables 7 and 8 show the pooled adverse event data and abnormal laboratory values from two single arm, open-label clinical trials, WV15376 (after the initial four weeks of randomized therapy) and WV15705. A total of 370 patients received maintenance therapy with valganciclovir tablets 900 mg q day. Approximately 252 (68%) of these patients received Valcyte tablets for more than nine months (maximum duration was 36 months).

Table 7. Pooled Selected Adverse Events Reported in ≥5% of Patients in Two Clinical Studies

Adverse Events According to Body System	% Patients N=370
Gastrointestinal system	
Diarrhea	41%
Nausea	30%
Vomiting	21%
Abdominal pain	15%
Body as a whole	
Pyrexia	31%
Headache	22%
Hemic and lymphatic system	
Neutropenia	27%
Anemia	26%
Thrombocytopenia	6%
Central and peripheral nervous system	
Insomnia	16%
Peripheral neuropathy	9%
Paresthesia	8%
Special senses	
Retinal detachment	15%

Serious adverse events reported from these two clinical trials (N=370) with a frequency of less than 5% and which are not mentioned in the two tables above, are listed below:

Hemic and lymphatic system: pancytopenia, bone marrow depression, aplastic anemia

Urogenital system: decreased creatinine clearance

Infections: local and systemic infections and sepsis

Bleeding complications: potentially life-threatening bleeding associated with thrombocytopenia

Central and peripheral nervous system: convulsion, psychosis, hallucinations, confusion, agitation

Body as a whole: valganciclovir hypersensitivity

Valcyte™ (valganciclovir HCl tablets)

Laboratory abnormalities reported with Valcyte tablets are listed below:

Table 8. Pooled Laboratory Abnormalities Reported in Two Clinical Studies

Laboratory Abnormalities	N=370
Neutropenia: ANC /μL	
<500	19%
500 – <750	17%
750 – <1000	17%
Anemia: Hemoglobin g/dL	
<6.5	7%
6.5 – <8.0	13%
8.0 – <9.5	16%
Thrombocytopenia: Platelets /μL	
<25000	4%
25000 – <50000	6%
50000 – <100000	22%
Serum Creatinine: mg/dL	
>2.5	3%
>1.5 – 2.5	12%

Experience with Ganciclovir

Valganciclovir is rapidly converted to ganciclovir upon oral administration. Adverse events reported with Valcyte in general were similar to those reported with ganciclovir (Cytovene). Please refer to the Cytovene label for more information on post-marketing adverse events associated with ganciclovir.

OVERDOSAGE

Overdose Experience With Valcyte Tablets

One adult developed fatal bone marrow depression (medullary aplasia) after several days of dosing that was at least 10-fold greater than recommended for the patient's estimated degree of renal impairment.

It is expected that an overdose of Valcyte tablets could also possibly result in increased renal toxicity (see PRECAUTIONS: General and DOSAGE AND ADMINISTRATION: Renal Impairment).

Since ganciclovir is dialyzable, dialysis may be useful in reducing serum concentrations in patients who have received an overdose of Valcyte tablets (see CLINICAL PHARMACOLOGY: Special Populations: *Hemodialysis*). Adequate hydration should be maintained. The use of hematopoietic growth factors should be considered (see CLINICAL PHARMACOLOGY: Special Populations: *Hemodialysis*).

Overdose Experience With Intravenous Ganciclovir

Reports of overdoses with intravenous ganciclovir have been received from clinical trials and during postmarketing experience. The majority of patients experienced one or more of the following adverse events:

Hematological toxicity: pancytopenia, bone marrow depression, medullary aplasia, leukopenia, neutropenia, granulocytopenia

Hepatotoxicity: hepatitis, liver function disorder

Renal toxicity: worsening of hematuria in a patient with pre-existing renal impairment, acute renal failure, elevated creatinine

Gastrointestinal toxicity: abdominal pain, diarrhea, vomiting

Neurotoxicity: generalized tremor, convulsion

DOSAGE AND ADMINISTRATION

Strict adherence to dosage recommendations is essential to avoid overdose. Valcyte tablets cannot be substituted for Cytovene capsules on a one-to-one basis.

Valcyte tablets are administered orally, and should be taken with food (see CLINICAL PHARMACOLOGY: Absorption). After oral administration, valganciclovir is rapidly and extensively converted into ganciclovir. The bioavailability of ganciclovir from Valcyte tablets is significantly higher than from ganciclovir capsules. Therefore the dosage and administration of Valcyte tablets as described below should be closely followed (see PRECAUTIONS: General and OVERDOSAGE).

For the Treatment of CMV Retinitis in Patients With Normal Renal Function

Induction:

For patients with active CMV retinitis, the recommended dosage is 900 mg (two 450 mg tablets) twice a day for 21 days with food.

Maintenance:

Following induction treatment, or in patients with inactive CMV retinitis, the recommended dosage is 900 mg (two 450 mg tablets) once daily with food.

Renal Impairment

Serum creatinine or creatinine clearance levels should be monitored carefully. Dosage adjustment is required according to creatinine clearance as shown in the table below (see PRECAUTIONS: General

and CLINICAL PHARMACOLOGY: Special Populations: *Renal Impairment*). Increased monitoring for cytopenias may be warranted in patients with renal impairment (see PRECAUTIONS: Laboratory Testing).

Table 9. Dose Modifications for Patients with Impaired Renal Function

CrCl* (mL/min)	Induction Dose	Maintenance Dose
≥ 60	900 mg twice daily	900 mg once daily
40 – 59	450 mg twice daily	450 mg once daily
25 – 39	450 mg once daily	450 mg every 2 days
10 – 24	450 mg every 2 days	450 mg twice weekly

*An estimated creatinine clearance can be related to serum creatinine by the following formulas:

$$\text{For males} = \frac{(140 - \text{age [years]}) \times (\text{body weight [kg]})}{(72) \times (\text{serum creatinine [mg/dL]})}$$

For females = 0.85 x male value

Hemodialysis Patients

Valcyte should not be prescribed to patients receiving hemodialysis (see CLINICAL PHARMACOLOGY: Special Populations: *Hemodialysis* and PRECAUTIONS: General).

Handling and Disposal

Caution should be exercised in the handling of Valcyte tablets. Tablets should not be broken or crushed. Since valganciclovir is considered a potential teratogen and carcinogen in humans, caution should be observed in handling broken tablets (see WARNINGS: Teratogenesis, Carcinogenesis and Mutagenesis). Avoid direct contact of broken or crushed tablets with skin or mucous membranes. If such contact occurs, wash thoroughly with soap and water, and rinse eyes thoroughly with plain water.

Because ganciclovir shares some of the properties of antitumor agents (ie, carcinogenicity and mutagenicity), consideration should be given to handling and disposal according to guidelines issued for antineoplastic drugs. Several guidelines on this subject have been published (see REFERENCES).

There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

HOW SUPPLIED

Valcyte (valganciclovir HCl tablets) is available as 450 mg pink convex oval tablets with "VGC" on one side and "450" on the other side. Each tablet contains valganciclovir HCl equivalent to 450 mg valganciclovir. Valcyte is supplied in bottles of 60 tablets (NDC 0004-0038-22).

Store at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [See USP controlled room temperature].

REFERENCES

1. Recommendations for the Safe Handling of Cytotoxic Drugs. US Department of Health and Human Services, National Institutes of Health, Bethesda, MD, September 1992. NIH Publication No. 92-2621

2. American Society of Hospital Pharmacists technical assistance bulletin on handling cytotoxic and hazardous drugs. *Am J Hosp Pharm.* 1990; 47:1033-1049

3. Controlling Occupational Exposures to Hazardous Drugs. US Department of Labor. Occupational Health and Safety Administration. OSHA Technical Manual. Section VI - Chapter 2, January 20, 1999

Valcyte tablets are manufactured by Patheon Inc., Mississauga, Ontario, Canada L5N 7K9

R_X only

Distributed by:

Valcyte™ (valganciclovir HCl tablets)

Roche Pharmaceuticals

Roche Laboratories Inc.
340 Kingsland Street
Nutley, New Jersey 07110-1199

27897552-0301

Issued: March 2001

Printed in USA

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-304

Roche Global Development-Palo Alto
Syntex (U.S.A.) LLC
Attention: Hermine Mante, PharmD.
Regulatory Program Manager
3401 Hillview Avenue
Palo Alto, California 94304-1397

Dear Dr. Mante:

Please refer to your new drug application (NDA) dated September 28, 2000, received September 29, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Valcyte (valganciclovir hydrochloride) 450 mg tablets.

We acknowledge receipt of your submissions dated:

October 9, 2000
November 16, 2000
November 27, 2000
December 1, 2000
January 9, 2001
January 16, 2001 (3)
January 19, 2001 (2)
January 26, 2001 (3)
January 30, 2001 (2)
January 31, 2001
February 2, 2001 (2)
February 5, 2001
February 6, 2001
February 7, 2001 (2)
February 13, 2001 (2)
February 15, 2001
February 16, 2001 (2)
February 19, 2001
February 20, 2001 (2)
February 22, 2001
March 6, 2001
March 8, 2001
March 13, 2001 (2)
March 14, 2001 (2)
March 15, 2001 (2)
March 16, 2001
March 20, 2001
March 22. 2001 (3)
March 23, 2001
March 26, 2001
March 27, 2001
March 28, 2001
March 29, 2001

This new drug application provides for the use of Valcyte (valganciclovir hydrochloride) 450 mg tablets for the treatment of cytomegalovirus (CMV) retinitis in patients with acquired immunodeficiency syndrome (AIDS).

We have completed the review of this application. We have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon labeling text. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the draft labeling submitted on March 29, 2001 and draft immediate container and carton labels in your submission dated March 14, 2001. Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit the FPL electronically according to the guidance for industry titled, *Providing Regulatory Submissions in Electronic Format - NDAs* (January 1999). For administrative purposes, this submission should be designated "FPL for approved NDA 21-304." In addition, please provide a clean text MS Word version of the label as a desk copy. Approval of this submission by FDA is not required before the labeling is used.

Alternatively, you may submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material.

In addition, we note the following postmarketing commitments in your submission dated March 23, 2001. These commitments include:

1. The applicant will commit to the timely completion and submission of study results from study PV 16000, "A Randomized, Double-Blind, Double-Dummy, Active-Comparator Controlled Multi-Center Study of the Efficacy and Safety of Valganciclovir Vs. Oral Ganciclovir for Prevention of Cytomegalovirus Disease in High-Risk Heart, Liver, and Kidney Allograft Recipients". The timing of this submission is estimated to be during the fourth quarter of 2002.

2. At the time that the efficacy supplement outlined above is submitted, the applicant will commit to submission of all available safety data collected in studies WV15376 and WV15705. The timing of this submission is estimated to be during the fourth quarter of 2002.

3. The applicant will commit to an analysis of the gender effects of valganciclovir and ganciclovir in ongoing studies, PV16000, WV15376 and WV15705.

Submit clinical protocols to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled **"Postmarketing Study Protocol", "Postmarketing Study Final Report", or "Postmarketing Study Correspondence."**

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). At this time, there are an insufficient number of pediatric AIDS patients with CMV retinitis to perform an adequate study to establish safety and efficacy in the pediatric population. Therefore, we are waiving the pediatric study requirement for this action on the indication in this application.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Leslie Stephens, Regulatory Project Manager, at (301) 827-2335.

Sincerely,

see next page

Debra B. Birnkrant, M.D.
Acting Director
Division of Antiviral Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

/s/

Debra Birnkrant
3/29/01 12:12:10 PM
NDA 21-304

US006083953A

United States Patent [19]

Nestor et al.

[11] Patent Number: 6,083,953

[45] Date of Patent: Jul. 4, 2000

[54] 2- (2-AMINO-1,6-DIHYDRO-6-OXO-PURIN-9-YL) METHOXY-1,3- PROPANEDIOL DERIVATIVE

[75] Inventors: **John Joseph Nestor**, Cupertino; **Scott William Womble**, Fremont; **Hans Maag**, Menlo Park, all of Calif.

[73] Assignee: **Syntex (U.S.A.) Inc.**, Palo Alto, Calif.

[21] Appl. No.: **08/812,991**

[22] Filed: **Mar. 4, 1997**

Related U.S. Application Data

[63] Continuation of application No. 08/453,223, May 30, 1995, abandoned, which is a continuation-in-part of application No. 08/281,893, Jul. 28, 1994, abandoned.

[51] **Int. Cl.**[7] **A61K 31/52**; C07D 473/18

[52] **U.S. Cl.** **514/262**; 544/276

[58] **Field of Search** 514/262; 544/276

[56] **References Cited**

U.S. PATENT DOCUMENTS

4,355,032	10/1982	Verheyden et al.	424/253
5,043,339	8/1991	Beauchamp	514/274

FOREIGN PATENT DOCUMENTS

0 158 847	10/1985	European Pat. Off. .
0 187 297	7/1986	European Pat. Off. .
0 249 248	12/1987	European Pat. Off. .
0 308 065	3/1989	European Pat. Off. .
0 375 329	6/1990	European Pat. Off. .
1 523 865	6/1978	United Kingdom .
2 104 070	3/1983	United Kingdom .
2 122 618	1/1984	United Kingdom .
8829571	6/1990	United Kingdom .
WO94/29311	12/1994	WIPO .

OTHER PUBLICATIONS

E. Jensen et al., "Synthesis, enzymatic hydrolysis and physico–chemical properties ... ", *Acta Pharm. Nord.*, 3(4), 243–247 (1991).

J.C. Martin et al., "Synthesis and Antiviral Activity of Various Esters ... ", *J. Pharm. Sci.*, 76(2), 180–184 (1987).

P.C. Maudgal et al., "Topical Treatment of Experimental Herpes Simplex Keratouveitis ... ", *Arch. Ophthalmol.*, 102, 140–142 (1984).

L. Colla et al., "Synthesis and Antiviral Activity of Water–soluble Esters of Acyclovir ... ", *J. Med. Chem.*, 26, 602–604 (1983).

L.M. Beauchamp et al., "Amino acid ester prodrugs of acyclovir", *Antiviral Chemistry & Chemotherapy*, 3(3), 157–164 (1992).

Primary Examiner—Mark L. Berch

Attorney, Agent, or Firm—Heller Ehrman White & McAuliffe

[57] **ABSTRACT**

The L-monovaline ester derived from 2-(2-amino-1,6-dihydro-6-oxo-purin-9-yl)methoxy-1,3-propanediol and its pharmaceutically acceptable salts are of value as antiviral agents with improved absorption.

6 Claims, No Drawings

2- (2-AMINO-1,6-DIHYDRO-6-OXO-PURIN-9-YL) METHOXY-1,3- PROPANEDIOL DERIVATIVE

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation of app. Ser. No. 08/453,223, abandoned filed May 30, 1995; which is in turn a continuation-in-part of app. Ser. No. 08/281,893, filed Jul. 28, 1994, now abandoned.

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates to a novel antiviral drug, particularly an amino acid ester of a purine derivative, and most particularly to an ester derived from ganciclovir and L-valine and pharmaceutically acceptable salts thereof. The invention also relates to intermediate compounds, synthetic methods for making the antiviral drug, and to methods of antiviral and related disease treatment, and pharmaceutical compositions therefor.

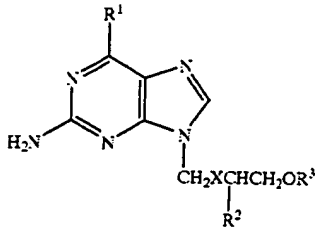
More specifically, the invention relates to the L-monovaline ester derived from 2-(2-amino-1,6-dihydro-6-oxo-purin-9-yl)methoxy-1,3-propanediol and its pharmaceutically acceptable salts.

2. Background Information

British Patent 1523865 describes antiviral purine derivatives with an acyclic chain in the 9-position. Among those derivatives 2-(2-amino-1,6-dihydro-6-oxo-1,6-dihydro-purin-9-yl)methoxy-ethanol with the INN name acyclovir has been found to have good activity against herpes viruses such as herpes simplex. While acyclovir has been found to be very effective upon topical or parenteral administration, it is only moderately absorbed upon oral administration.

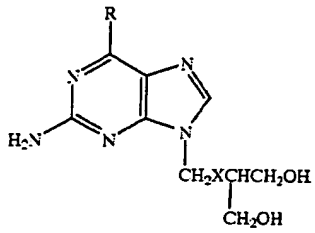
U.S. Pat. No. 4,355,032 discloses the compound 9-[(2-hydroxy-1-hydroxymethyl-ethoxy)methyl]-guanine or 2-(2-amino-1,6-dihydro-6-oxo-purin-9-yl)methoxy-1,3-propanediol with the INN name ganciclovir. Ganciclovir is highly efficacious against viruses of the herpes family, for example, against herpes simplex and cytomegalovirus. It has a relatively low rate of absorption when administered orally and must be used at high dosages when administered by that route. Ganciclovir is most commonly administered via intravenous infusion. This mode of administration has the disadvantage of being very inconvenient to the patient, often requiring the services of a doctor, nurse or other health care professional. There is also a certain risk of infection which is particularly problematic for immunocompromised patients who receive treatment with ganciclovir and may have little resistance against infections. Therefore it has been highly desirable to provide ganciclovir with an improved oral absorption profile.

British Patent Application GB 2 122 618 discloses derivatives of 9-(2-hydroxyethoxymethyl)guanine of the generic formula



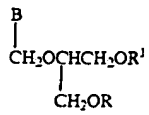
wherein X represents an oxygen or sulphur atom, R^1 represents a hydroxy or an amino group, R^2 represents a hydrogen atom or a group of the formula $—CH_2OR^3{}_a$ and R^3 and $R^3{}_a$ may be the same or different, each represents an amino acid acyl radical and physiologically acceptable salts thereof. These compounds are useful for the treatment of viral infections and have high water solubility which renders them of value in the formulation of aqueous pharmaceutical preparations. While the generic formula in the British patent application includes compounds in which R^2 is the group $—CH_2OR^3{}_a$, specific compounds of this group are not disclosed. The patent application also discloses that formulations used with these compounds with improved water-solubility include oral, rectal, nasal, topical, vaginal or parenteral formulations.

British Patent Application GB 2 104 070 A discloses antiviral compounds of the formula



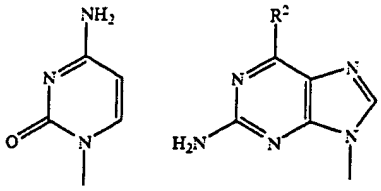
wherein R is a hydroxy or amino group and X is an oxygen or sulphur atom and physiologically acceptable salts and esters. The general formula includes ganciclovir and physiologically acceptable salts and esters. The esters include those containing a formyloxy group, C_{1-16} (for example, C_{1-6}) alkanoyloxy (e.g. acetoxy or propionyloxy), optionally substituted aralkanoyloxy (e.g. phenyl-C_{1-4} alkanoyloxy such as phenylacetoxy) or optionally substituted aroyloxy (e.g. benzoyloxy or naphthoyloxy) ester grouping at one or both of the terminal positions of the 9-side chain of the compounds of the general formula. The above-mentioned aralkanoyloxy or aroyloxy ester groups may be substituted, for example by one or more halogen (e.g. chlorine or bromo atoms) or amino, nitrile or sulphamido groups, the aryl moiety of the grouping advantageously containing 6 to 10 carbon atoms.

European Patent Application EP 0 375 329 discloses prodrug compounds with the following formula



wherein R and R^1 are independently selected from a hydrogen atom and an amino acyl residue providing at least one

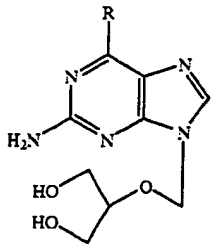
of R and R^1 represents an amino acid acyl residue and B represents a group of the formulae



in which R^2 represents a C_{1-6} straight chain, C_{3-6} branched chain or C_{3-6} cyclic alkoxy group, or a hydroxy or amino group or a hydrogen atom and the physiologically acceptable salts thereof. These prodrug compounds are described as having advantageous bioavailability when administered the oral route, resulting in high levels of the parent compound in the body.

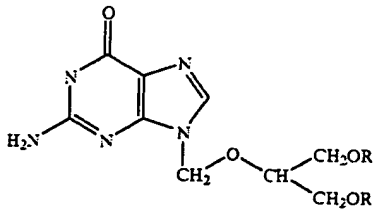
Example 3b) European Patent Application EP 0 375 329 discloses the preparation of the bis(L-isoleucinate) ester of ganciclovir as white foam. Example 4b) discloses the preparation of the bis(glycinate) ester of ganciclovir as a white solid. Example 5b) discloses the preparation of the bis (L-valinate) ester of ganciclovir as a solid. Example 6b) discloses the preparation of the bis(L-alaninate) ester of ganciclovir as a syrup containing 90% of the bis ester and 10% of the monoester. The described bis esters are non-crystalline materials which are difficult to process for the manufacture of oral pharmaceutical dosage forms.

British Patent Application No. 8829571 discloses amino acid esters of the compounds of the formula

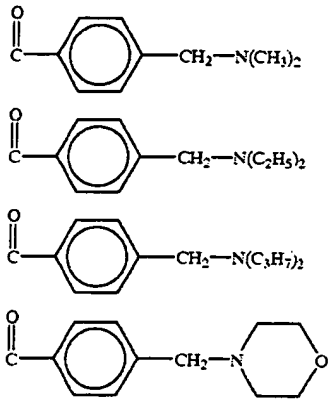


(wherein R represents a hydroxy or amino group or a hydrogen atom) and the physiologically acceptable salts thereof. Examples of preferred amino acids include aliphatic acids e.g. containing up to 6 carbon atoms such as glycine, alanine, valine and isoleucine. The amino acid esters include both, mono and diesters. However, this patent application as well as European Patent Publication 375 329 and U.S. Pat. No. 5,043,339 do not disclose the preparation of monoesters, much less any data suggesting their usefulness.

E. Jensen et. al., *Acta Pharm. Nord.* 3(4) 243–247 (1991) disclose the synthesis, enzymatic hydrolysis and physicochemical properties of N-substituted 4-(aminomethyl) benzoate diester prodrugs of ganciclovir of the formula



wherein R can be



These esters were synthesized and evaluated with the aim of improving the delivery characteristics of ganciclovir. The esters were hydrolyzed enzymatically by human plasma to the parent drug, the hydrolysis proceeding through formation of the corresponding monoester. The authors evaluated these esters in terms of their rate of enzymatic hydrolysis, lipophilicity and concluded that the properties of these esters make the diesters a promising prodrug type for ganciclovir to enhance its delivery characteristics for e.g. parenteral administration.

John C. Martin et. al., *J. Pharm. Sci.* 76(2), p.180–184 disclose mono- and diacyl esters of ganciclovir which were tested to examine their bioavailability after oral administration. The authors indicate that the dipropionate ester is about 42% more bioavailable than ganciclovir itself.

European Patent Application 0 158 847 discloses inter alia that 6-deoxy-acyclovir and 6-deoxy-ganciclovir can be readily converted in vivo by the action of enzymes into acyclovir and ganciclovir, respectively. From experiments in rats the inventors found that oral administration of these 6-deoxy prodrugs results in efficient absorption from the gastro-intestinal tract and high plasma levels of the parent drugs.

P. C. Maudgal et. al., *Arch. Opthalmol.* 1984; 102: 140–142 disclose the glycine ester of acyclovir as efficacious in the topical treatment of epithelial and stromal herpes simplex keratitis and associated iritis when administered as a 1% eye drop formulation to rabbits. The authors disclose the glycine, alanine, β-alanine and succinyl esters of acyclovir and indicate that the solubility of the glycine ester is about 30-fold greater than the solubility of acyclovir itself, which permits the use of the glycine ester for eye drops with concentrations up to 6%, while acyclovir itself is used as ointment which is hardly effective in stromal disease or iritis.

Leon Colla et. al., *J. Med. Chem.* 98. 3, 26, 602–604 disclose several water-soluble ester derivatives of acyclovir and their salts as prodrugs of acyclovir. The authors indicate

that acyclovir cannot be given as eye drops or intramuscular injections because of its limited solubility in water and have therefore synthesized derivatives of acyclovir which are more water soluble than the parent compound. The authors disclose the hydrochloride salt of the glycyl ester, the hydrochloride salt of the alanyl ester, the hydrochloride salt of the β-alanyl ester, the sodium salt of the succinyl ester, and the azidoacetate ester. When assayed in primary rabbit kidney cell cultures against various herpes simplex virus type 1 and type 2 strains, according to the authors, the first four esters proved almost as active as acyclovir itself. The authors suggest that these acyclovir esters should be more practical for clinical use than the parent compound for topical treatment as eye drops and for systemic treatment of herpes virus infections that respond well to intravenous acyclovir treatment. In contrast with acyclovir, these esters could be given in much smaller volumes, and therefore via intramuscular injections.

L. M. Beauchamp et. al., *Antiviral Chemistry & Chemotherapy* (1992), 3 (3), 157–164 disclose eighteen amino acid esters of the antiherpetic drug acyclovir and their efficiencies as prodrugs of acyclovir, evaluated in rats by measuring the urinary recovery of acyclovir. Ten prodrugs produced greater amounts of the parent drug in the urine than acyclovir itself: the glycyl, D,L-alanyl, L-alanyl, L-2-aminobutyrate, D,L-valyl, L-valyl, DL-isoleucyl, L-isoleucyl, L-methionyl, and L-prolyl ester. The L-amino acid esters were better prodrugs than the corresponding D- or D,L-isomers, suggesting the involvement of a stereoselective transporter. From Table 1 of the publication which provides chemical data and oral bioavailability of the eighteen amino acid esters it follows that the D-amino acid esters have a lower oral bioavailability than acyclovir itself. Therefore, because the D-amino acid esters have no benefit over acyclovir they are not useful as prodrugs of acyclovir. The achiral glycyl ester of acyclovir, however, has a higher oral bioavailability than acyclovir (in the urinary recovery assay 30% of the acyclovir dosed as glycyl ester was recovered, whereas with acyclovir dosing 19% of the acyclovir was recovered). According to the authors the L-valyl ester of acyclovir was the best prodrug of the esters investigated.

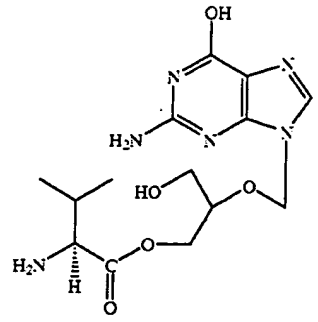
European Patent Publication 308 065 discloses the valine and isoleucine esters of acyclovir, preferably in the L-form, as showing a large increase in absorption from the gut after oral administration, when compared with other esters and acyclovir.

Currently the leading drug for the treatment of cytomegalovirus infection is ganciclovir. However, its very limited oral bioavailability and the need for slow daily intravenous infusion of the drug (or for intravitreal injections or implants) indicate the urgent need for an oral dosage form with improved bioavailability.

The present invention provides a stable prodrug formulation of ganciclovir with improved oral absorption and low toxicity. Such characteristics are especially valuable for suppression of herpetic infections in immunocompromised patients where oral administration therapeutically is the preferred choice. In addition, the active ingredients exhibit pharmacopoeial properties which permit their improved characterization and pharmaceutical processing. Surprisingly, it was found that the L-monovaline ester of ganciclovir and its pharmaceutically acceptable salts exhibit these desired characteristics.

SUMMARY OF THE INVENTION

In a first aspect, this invention provides the compound of the formula I:

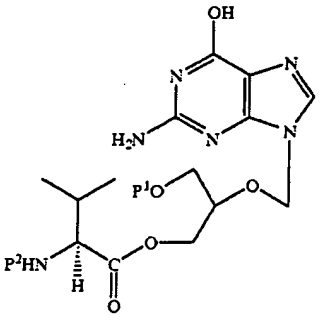


and pharmaceutically acceptable salts thereof. The compound is named hereinafter 2-(2-amino-1,6-dihydro-6-oxopurin-9-yl)methoxy-3-hydroxy-1-propanyl-L-valinate or mono-L-valine ganciclovir.

In a second aspect, this invention provides a pharmaceutical composition which contains the mono-L-valine ester of ganciclovir or a pharmaceutically acceptable salt or diastereomer thereof, preferably in admixture with one or more suitable excipients or carriers.

In a third aspect, this invention provides a method of treating or preventing viral infections or related diseases comprising the administration of the mono-L-valine ester of ganciclovir or a pharmaceutically acceptable salt thereof or a composition containing same to an animal in need of such treatment or prevention.

In a fourth aspect, this invention provides compounds of Formula II which are useful intermediates for preparing mono-L-valine ganciclovir and its pharmaceutically acceptable salts:



wherein P_1 is a hydroxy-protecting group and P_2 is an amino-protecting group.

A fifth aspect of this invention is a process for preparing the prodrug compound of the invention and its pharmaceutically acceptable salts. This process involves the esterification of ganciclovir and its derivatives, the removal of protecting groups from ganciclovir bis L-valine ester to the mono-L-valine ester of Formula I, the condensation of guanine with a substituted glycerol, the optical resolution of a compound of the Formula I, and the formation of salts of the prodrug of Formula I. Details of the process are described below.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

Unless otherwise stated, the following terms used in the specification and claims have the meanings given below:

"Alkyl" means a straight or branched saturated hydrocarbon radical having from one to the number of carbon atoms designated. For example, C_{1-7} alkyl is alkyl having at least one but no more than seven carbon atoms, e.g. methyl, ethyl, i-propyl, n-propyl, n-butyl,n-pentyl, n-heptyl and the like.

"Lower alkyl" means an alkyl of one to six carbon atoms.

"Aryl" means an organic radical derived from an aromatic hydrocarbon by the removal of one hydrogen atom. Preferred aryl radicals have six to twelve carbon atoms as ring carbon atoms in the aromatic hydrocarbon.

"Aralkyl" means an organic radical derived from an aralkane in which an alkyl hydrogen atom is substituted by an above-defined aryl group.

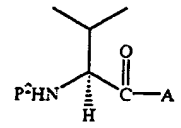
"Acyl" means an organic radical derived from an organic acid by the removal of the hydroxyl group; e.g., CH_3CO— is the acyl radical of CH_3COOH, or acetyl. Other examples for such acyl groups are propionyl, or benzoyl, etc. The term "acyl" includes the term "alkanoyl" which is the organic radical RCO— in which R is an alkyl group as defined above.

"Lower alkoxy", "(lower alkyl)amino", "di(lower alkyl) amino", "(lower alkanoyl)amino", and similar terms mean alkoxy, alkylamino, dialkylamino, alkanoylamino, etc. in which the or each alkyl radical is a "lower alkyl" as described above.

"Halogen" means fluorine, chlorine, bromine, or iodine.

According to Hackh's *Chemical Dictionary,* McGraw-Hill Book Company, 1969, "derivative" of a compound means a compound obtainable from the original compound by a simple chemical process.

"Activated derivative" of a compound means a reactive form of the original compound which renders the compound active in a desired chemical reaction, in which the original compound is only moderately reactive or non-reactive. Activation is achieved by formation of a derivative or a chemical grouping within the molecule with a higher free energy content than that of the original compound, which renders the activated form more susceptible to react with another reagent. In the context of the present invention activation of the carboxy group is of particular importance and corresponding activating agents or groupings which activate the carboxy group are described in more detail below. An example of an activated derivative of L-valine is the compound of Formula III



wherein P^2 is an amino-protecting group and A is a carboxy-activating group, for example, halo or a lower acyloxy group. A further example is an amino acid anhydride which is an activated form of an amino acid which renders the amino acid (especially L-valine) susceptible to esterification. Another example are UNCA's described in more detail below.

"Protecting group" means a chemical group that (a) preserves a reactive group from participating in an undesirable chemical reaction; and (b) can be easily removed after protection of the reactive group is no longer required. For example, the benzyl group is a protecting group for a primary hydroxyl function.

"Amino-protecting group" means a protecting group that preserves a reactive amino group that otherwise would be modified by certain chemical reactions. The definition includes the formyl group or lower alkanoyl groups with 2 to 4 carbon atoms, in particular the acetyl or propionyl group, the trityl or substituted trityl groups, such as the monomethoxytrityl group, dimethoxytrityl groups such as the 4,4'-dimethoxytrityl or 4,4'-dimethoxytriphenylmethyl group, the trifluoroacetyl, and the N-(9-fluorenylmethoxycarbonyl) or "FMOC" group, the allyloxycarbonyl group or other protecting groups derived from halocarbonates such as (C_6–C_{12})aryl lower alkyl carbonates (such as the N-benzyloxycarbonyl group derived from benzylchlorocarbonate), or derived from biphenylalkyl halo carbonates, or tertiary alkyl halo carbonates, such as tertiary-butylhalocarbonates, in particular tertiary butylchlorocarbonate, or di(lower)alkyldicarbonates, in particular di(t-butyl)-dicarbonate, and the phthalyl group.

"Hydroxy-protecting group" means a protecting group that preserves a hydroxy group that otherwise would be modified by certain chemical reactions. Suitable hydroxy-protecting groups include ether-forming groups that can be removed easily after completion of all other reaction steps, such as the benzyl or the trityl group optionally substituted in their phenyl ring. Other suitable hydroxy-protecting groups include alkyl ether groups, the tetrahydropyranyl, silyl, trialkylsilyl ether groups and the allyl group.

"Leaving group" means a labile group that is replaced in a chemical reaction by another group. Examples of leaving groups are halogen, the optionally substituted benzyloxy group, the isopropyloxy group, the mesyloxy group, the tosyloxy group or the acyloxy group.

All the activating and protecting agents employed in the preparation of the compound of Formula I must meet the following qualifications: (1) their introduction should proceed quantitatively and without racemization of the L-valine component; (2) the protecting group present during the desired reaction should be stable to the reaction conditions to be employed; and (3) the group must be readily removed under conditions in which the ester bond is stable and under which racemization of the L-valine component of the ester does not occur.

The term "chirality" means the property of handedness ascribed to a molecule which describes the symmetry elements of the molecule (or the absence of symmetry elements). Molecules that lack symmetry elements are "chiral". A chiral molecule lacking all of the symmetry elements, even including a simple axis, is termed "asymmetric".

The term "achiral" means the presence of at least one symmetry element in a molecule, such as a simple axis.

"Isomerism" refers to compounds having the same atomic mass and atomic number but differing in one or more physical or chemical properties. Various types of isomers include the following:

"Stereoisomer" refers to a chemical compound having the same molecular weight, chemical composition, and constitution as another, but with the atoms grouped differently. That is, certain identical chemical moieties are at different orientations in space and, therefore, when pure, have the ability to rotate the plane of polarized light. However, some pure stereoisomers may have an optical rotation that is so slight that it is undetectable with present instrumentation.

"Optical isomer" describes one type of stereo isomerism which manifests itself by the rotation that the isomer, either pure or in solution, imparts to the plane of polarized light. It is caused in many instances by the attachment of four different chemical atoms or groups to at least one of the carbon atoms in a molecule, or expressed alternatively, by the above-described chirality of the molecule.

Stereoisomers or optical isomers that are mirror images of one another are termed "enantiomers" and may be said to be enantiomeric. Chiral groups that are mirror images of one another are termed enantiomeric groups.

Enantiomers whose absolute configurations are not known may be differentiated as dextrorotatory (prefix+) or laevorotatory (prefix−) depending on the direction in which, under specified experimental conditions, they rotate the plane of polarized light.

When equal amounts of enantiomeric molecules are present together, the product is termed racemic, independently of whether it is crystalline, liquid, or gaseous. A homogeneous solid phase composed of equimolar amounts of enantiomeric molecules is termed a racemic compound. A mixture of equimolar amounts of enantiomeric molecules present as separate solid phases is termed a racemic mixture. Any homogeneous phase containing equimolar amounts of enantiomeric molecules is termed a racemate.

Compounds which have two asymmetric carbon atoms (chiral centers) have four stereoisomers which form two pairs of enantiomers. Whereas the enantiomers of a pair are mirror images of each other, the enantiomers of the two separate pairs are not mirror images of each other and are called "diastereomers". Diastereomers have similar but not identical chemical properties and have different physical properties, e.g. melting points, solubility, etc.

The optically active compounds herein can be designated by a number of conventions; i.e., the R- and S-sequencing rules of Cahn and Prelog; erythro and threo isomers; D and L-isomers; d and l-isomers; and (+) and (−) isomers, which indicates the direction a plane of polarized light is rotated by the chemical structure, either pure or in solution. These conventions are well known in the art and are described in detail by E. L. Eliel in *Stereochemistry of Carbon Compounds,* published by McGraw Hill Book Company, Inc. of New York in 1962 and references cited therein. Thus, these isomers may be described as d-, l- , or a d,l-pair; or D-, L-, or a D,L-pair; or R-, S-, or an R,S-pair; depending upon the nomenclature system employed. In general, this application will use the (D), (L) and (D,L) designation for the amino acid (valine), and the (R), (S) and (R,S) designation for the asymmetric carbon in the ganciclovir moiety to distinguish between the two.

The compound of Formula I and the compounds of Formula II have two asymmetric enters (2 carbon atoms), one in the valine component and the other in the aliphatic side chain of the ganciclovir component. The latter is the carbon atom 2 of the propanyl radical. Therefore the compound of Formula I and the compounds of Formula II exist as diastereomers and as mixtures of diastereomers. As concerns the compounds of the invention, any diastereomer or mixture of diastereomers may be used and the claims are intended to cover the individual diastereomers and mixtures thereof, unless otherwise restricted. Formula I includes the two diastereomers of Formula I, as well as mixtures thereof.

"Optional" or "optionally" means that a described event or circumstance may or may not occur, and that the description includes instances where said event or circumstance occurs and instances in which it does not. For example, "optionally substituted phenyl" means that the phenyl may or may not be substituted and that the description includes both unsubstituted phenyl and phenyl wherein there is substitution; "optionally followed by converting the free base to the acid addition salt" means that said conversion may or may not be carried out in order for the process described to fall within the invention, and the invention includes those processes wherein the free base is converted to the acid addition salt and those processes in which it is not.

"Pharmaceutically acceptable" means that which is useful in preparing a pharmaceutical composition that is generally safe and non-toxic and includes that which is acceptable for veterinary use as well as human pharmaceutical use.

"Pharmaceutically acceptable salts" means salts which possess the desired pharmacological activity and which are neither biologically nor otherwise undesirable. Such salts include acid addition salts formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or with organic acids such as acetic acid, propionic acid, hexanoic acid, heptanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, o-(4-hydroxy-benzoyl)-benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethanedisulfonic acid, 2-hydroxyethane-sulfonic acid, benzenesulfonic acid, p-chlorobenzenesulfonic acid, 2-naphthalenesulfonic acid, p-toluenesulfonic acid, camphorsulfonic acid, 4-methyl-bicyclo[2.2.2]oct-2-ene1-carboxylic acid, gluco-heptonic acid, 4,4'-methylenebis(3-hydroxy-2-naphthoic) acid, 3-phenylpropionic acid, trimethyl-acetic acid, tertiary butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxy-naphthoic acids, salicylic acid, stearic acid, muconic acid, and the like. Preferred pharmaceutically acceptable salts are those formed with hydrochloric, sulfuric, phosphoric acid, acetic or methanesulfonic acid, ethanesulfonic acid, 1,2-ethanedisulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, p-chlorobenzenesulfonic acid, and 2-naphthalenesulfonic acid, p-toluenesulfonic acid, camphorsulfonic acid.

Synthetic Reaction Parameters

Unless specified to the contrary, the reactions described herein take place at atmospheric pressure within a temperature range from 5° C. to 170° C. (preferably from 10° C. to 50° C.; most preferably at "room" or "ambient" temperature, e.g., 20–30° C.). However, there are clearly some reactions where the temperature range used in the chemical reaction will be above or below these temperature ranges. Further, unless otherwise specified, the reaction times and conditions are intended to be approximate, e.g., taking place at about atmospheric pressure within a temperature range of about 5° C. to about 100° C. (preferably from about 10° C. to about 50° C.; most preferably about 20° C.) over a period of about 1 to about 100 hours (preferably about 5 to 60 hours). Parameters given in the Examples are intended to be specific, not approximate.

Isolation and purification of the compounds and intermediates described herein can be effected, if desired, by any suitable separation or purification procedure such as, for example, filtration, extraction, crystallization, column chromatography, thin-layer chromatography or thick-layer chromatography, or a combination of these procedures. Specific illustrations of suitable separation and isolation procedures can be had by reference to the examples hereinbelow. However, other equivalent separation or isolation procedures can, of course, also be used.

Medical Definitions

"Animal" includes humans, non-human mammals (such as dogs, cats, rabbits, cattle, horses, sheep, goats, swine, and deer) and non-mammals such as birds, fish and the like.

"Disease" specifically includes any unhealthy condition of an animal or part thereof. Thus, "disease" here includes

any viral or related disease that is treatable with mono-L-valine ganciclovir or pharmaceutically acceptable salts thereof.

"Treatment" means any treatment of a disease in an animal and includes:

(1) preventing the disease from occurring in an animal which may be predisposed to the disease but does not yet experience or display symptoms of the disease; e.g., prevention of the outbreak of the clinical symptoms;

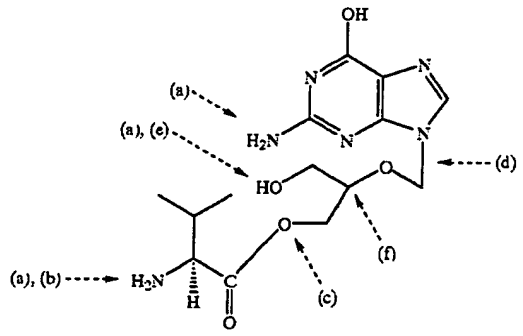
(2) inhibiting the disease, e.g., arresting its development; or

(3) relieving the disease, e.g., causing regression of the symptoms of the disease.

"Effective amount" for the treatment of a disease means that amount which, when administered to an animal in need thereof, is sufficient to effect treatment, as defined above, for that disease.

Processes for Preparing Compounds of the Invention

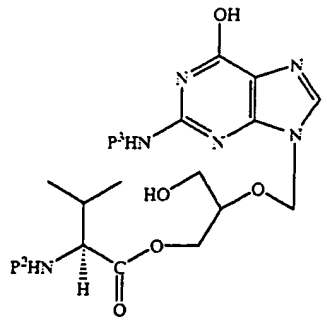
The compound of Formula I or its pharmaceutically acceptable salts are prepared by a variety of methods. The synthetic approaches are apparent from the labelled dotted lines [(a) through (f)] in Formula I below. The dotted lines point schematically to the respective reaction sites and the ensuing table gives a brief description of the various methods that will be described in more detail below. The letter symbols in parentheses refer to the respective step in the process description/claim(s):



Approach	Method
(a)	De-protectian
(b)	Salt Formation
(c)	Esterification
(d)	Condenesation
(e)	Partial Hydrolysis
(f)	Optical Resolution/Diastereomer Separation

Accordingly, the process for the preparation of the compound of Formula I or a pharmaceutically acceptable salt thereof comprises one or more of the following steps:

(a) removal of an amino- and/or hydroxy-protecting group from a compound with the Formula IV

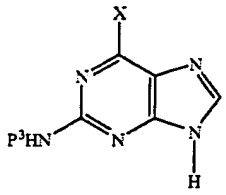


wherein P^1 is a hydroxy-protecting group or hydrogen, P^2 is an amino-protecting group, and P^3 is hydrogen or P^2 to afford the compound of Formula I;

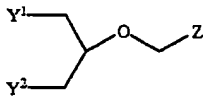
(b) conversion of the compound of Formula I into a pharmaceutically acceptable salt thereof;

(c) esterification of 2-(2-amino-1,6-dihydro-6-oxo-purin-9-yl)methoxy-1,3-propanediol (ganciclovir) or a salt thereof, with an activated derivative of L-valine;

(d) condensation of an optionally substituted guanine of the Formula (V)



optionally in persilylated form,
wherein P^3 is hydrogen or an amino-protecting group, with a 2-substituted glycerol of the Formula (VI)


(V)

wherein Y^1 and Y^2 independently are halo, lower acyloxy, lower alkyloxy, or aralkyloxy groups, and Z is a leaving group selected from lower acyloxy, methoxy, isopropyloxy, benzyloxy, halo, mesyloxy or tosyloxy, and the like; optionally in the presence of a Lewis acid catalyst, to provide the compound of Formula I; or

(e) partial hydrolysis of the bis ester 2-(2-amino-1,6-dihydro-6-oxo-purin-9-yl)methoxy-1,3-propanediyl bis (L-valinate) or a salt thereof to afford the monoester of the Formula I; or

(f) optical resolution or diastereomeric separation of a compound of Formula (I).

Utility and Testing

The compound of Formula I and its pharmaceutically acceptable salts exhibit pharmaceutical activity and in particular antiviral activity. As such, the compound and its pharmaceutically acceptable salts are useful for treating a broad range of conditions in animals, particularly humans.

Examples of conditions that may be treated using the compound and salts of this invention include herpes infec-

tions such as herpes types 1, 2 and 6, varicella Zoster, Eppstein-Barr virus, and in particular cytomegalovirus, and hepatitis B and related viruses, in humans or non-human animals, particularly in humans. Examples of clinical conditions caused by these viruses are herpetic keratitis, herpetic encephalitis, cold sores, genital infections (caused by herpes simplex), chicken pox, shingles (caused by varicella Zoster), CMV-pneumonia and -retinitis, particularly in immunocompromised patients including transplant recipients (for example, heart, renal and bone marrow transplants) and patients with Acquired Immune Deficiency Syndrome (AIDS), Eppstein-Barr virus-caused infectious mononucleosis. The compound of the invention is also useful for the treatment of certain carcinomas or lymphomas caused by, or related to, viral infections, such as nasopharyngeal cancer, immunoblastic lymphoma, Burkitt's lymphoma, and hairy leukoplakia.

In summary, then another aspect of this invention is a method for treating an animal (preferably a human) exhibiting a condition in which an above-described viral infection plays a role, or prophylactically treating an animal where such viral infection is anticipated by the treating physician or veterinarian. The method comprises administering a therapeutically effective amount of mono-L-valine ganciclovir or its pharmaceutically acceptable salts to such animal. A therapeutically effective amount of the compound or its pharmaceutically acceptable salts is an amount that is efficacious in treating the condition, i.e. the disease. The exact amount administered may vary over a wide range depending on the degree of severity of the specific condition being treated, age and weight of the subject, relative health of the subject and other factors (such as type of formulation). For an oral formulation a therapeutically effective amount may vary from about 1 to 250 mg per Kg body weight per day, preferably about 7 to 100 mg/Kg body weight per day. Most preferably the therapeutically effective amount is about 10 to 50 mg/Kg/day, especially for the treatment of CMV retinitis and pneumonia. Thus, for a 70 Kg human, a therapeutically effective amount is from about 70 mg/day to about 7 g/day, preferably about 500 mg/day to about 5 g/day, most preferably 700 mg/day to 3.5 g/day. For an intravitreal implant, however, the does of the prodrug will range from 0.5 mg to 25 mg, preferably from 5 to 10 mg per implant. It is well understood by those skilled in the art that different dosage forms of the prodrugs of the invention will command different dosage ranges.

Ganciclovir is a proven antiviral drug. The utility of the ganciclovir prodrug of the present invention has been established by determining the blood level concentrations of ganciclovir in test animals (the rat and the monkey), following oral administration of the prodrug. The blood plasma level concentrations were determined according to the methods described in Examples 9 and 10 and are procedures which modified procedures described by Jean-Pierre Sommadossi et. al. in *REVIEWS OF INFECTIOUS DISEASES*, VOL. 10, SUPPLEMENT 3, p. S507 and in *Journal of Chromatography, Biomedical Applications*, 414 (1987), 429–433.

Administration and Pharmaceutical Composition

The compound or its pharmaceutically acceptable salts of this invention may be administered via any of the usual and acceptable modes known in the art, either singly or in combination with another therapeutic agent. Generally the compound and salts of this invention are administered as a pharmaceutical composition with a pharmaceutically acceptable excipient and are administered orally, systemically (e.g. transdermally, or by suppository) or parenterally (e.g. intramuscularly [im], intravenously [iv], subcutaneously [sc]) or intravitreally by an implant. The compound of the invention can thus be administered in a composition that is a semisolid, powder, aerosol, solution, suspension or other appropriate composition, as discussed hereinafter. Oral pharmaceutical compositions are preferred.

A pharmaceutical composition comprises the compound of Formula I or its pharmaceutically acceptable salts, preferably in combination with a pharmaceutically acceptable excipient. Such excipient is one that is non-toxic. Such excipient may be any solid, liquid, semisolid, gaseous (in case of an aerosol) excipient that is generally available to one of skill in the art and that does not adversely affect the activity of the active agent.

In general, the pharmaceutical composition of this invention will contain a therapeutically effective amount of the compound or its pharmaceutically acceptable salts in combination with at least one excipient. Depending on the type of formulation, size of a unit dosage, kind of excipients and other factors known to those of sill in the art of pharmaceutical sciences the amount of compound of this invention may vary over a wide range in the composition. In general, the final composition will comprise about 1% to about 99.5% wt of a compound of the invention with the remainder being the excipient or excipients. Preferably the level of active compound will be about 10.0% wt to about 99.% wt and most preferably about 50% wt to about 99% wt, with the remainder being a suitable excipient or excipients. Useful pharmaceutical excipients for the preparation of the pharmaceutical compositions hereof can be solids, semisolids, liquids or gases. Thus, the compositions can take the form of tablets, pills, capsules, powders, suppositories, transdermal patches, sustained release formulations, intravitreal implants, solutions, in particular intravenous solutions, suspensions, elixirs, aerosols, and the like. Solid pharmaceutical excipients include starches, such as corn starch, cellulose, talc, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, magnesium stearate, sodium stearate, stearic acid, glycerol monostearate, sodium chloride, dried skim milk, and the like. Liquid and semisolid excipients may be selected from water, ethanol, glycerol, propylene glycol, various oils, including those of petroleum, animal, vegetable or synthetic origin, for examples, peanut oil, soybean oil, mineral oil, sesame oil, and the like. Water, saline, aqueous dextrose, and glycols are preferred liquid carriers, particularly for injectable solutions. Other suitable pharmaceutical excipients and carriers and their formulations are described in *"Remington's Pharmaceutical Sciences"* by E. W. Martin, incorporated herein by reference.

Preferably the pharmaceutical composition is administered in a single unit dosage form, more preferably an oral dosage form, for continuous treatment or in a single unit dosage form ad libitum when relief of symptoms is specifically required.

Presently Preferred Embodiments

While the broadest definition of this invention is set forth in the Summary of the Invention as the compound of Formula I and its pharmaceutically acceptable salts, the (R,S) mixture and certain salts are preferred.

The following acids are preferred to form pharmaceutically acceptable salts with the compound of Formula I: hydrochloric, sulfuric, phosphoric acid, acetic, methanesulfonic, ethanesulfonic, 1,2-ethanedisulfonic, 2-hydroxyethanesulfonic, benzenesulfonic,

p-chlorobenzenesulfonic, 2-naphthalenesulfonic, p-toluenesulfonic and camphorsulfonic acid. Most preferred are strong inorganic acids, such as hydrochloric, sulfuric or phosphoric acid.

The most preferred compounds are 2-(2-amino-1,6-dihydro-6-oxo-purin-9-yl)methoxy-3-hydroxy-1-propanyl L-valinate hydrochloride and acetate. These compounds can be prepared as crystalline materials and therefore can be easily manufactured into stable oral formulations. Oral and intravenous formulations are preferred. The oral formulations have the advantage of high bioavailability; the intravenous formulations have the advantage that the prodrug of the invention, unlike intravenous ganciclovir formulations be prepared using a physiologically more acceptable pH (4–6). The intravenous formulation of ganciclovir requires a pH of 11 which results in irritation.

It is understood that these compounds are particularly useful in the pharmaceutical compositions and methods of treatment of this invention.

In any of the last step processes described herein, a reference to Formula I, II, III, IV, V or VI refers to such Formulae wherein P^1, P^2, and P^3, A, Y^1, Y^2 and Z are as defined in their broadest definitions set forth in the Summary of the Invention, with the processes applying particularly to the presently preferred embodiments.

The preferred pharmaceutical compositions of this invention contain a pharmaceutically acceptable salt of the prodrug of Formula I. Accordingly, if the manufacture of pharmaceutical formulations involves intimate mixing of the pharmaceutical excipients and the active ingredient in its salt form, then it is preferred to use pharmaceutical excipients which are non-basic in nature, i.e., either acidic or neutral.

Details of the Synthetic Processes

The currently preferred process for producing the compound of the Formula I involves step (a), preferably carried out with the concomitant formation of a salt of a compound of Formula I, or step (c), or a combination of steps (a) and (c). (See the description of Steps III and IV below). The preparation of the monoester according to step (a) requires the selective protection of one of the two primary hydroxyl functions of ganciclovir or its derivative. This generally may or may not involve protection of the amino group in the 2-position of the guanine base (see the detailed description below of Steps I through III for the case the process is carried out with a protected amino group). In addition, before the esterification (Step III) is carried out, the amino group of the amino acid reagent must be protected, to avoid its interference (amide formation) in the esterification reaction. The protection of the amino group is described in the section "Preparation of the N-Protected Amino Acid" below.

In general, when carrying out a process of this invention, those amino, hydroxy or carboxylic groups which are not to participate in the synthesis reaction must be protected until (1) either de-protection yields the final product; or (2) a specific protected group is to be involved in the next synthetic step; or (3) the presence of the unprotected group in the ensuing reaction steps leading to the final product would not modify the intended sequence of reactions. An example for meeting requirement (1) is the benzyl group in the preparation of the monoesters of this invention, which protects one primary hydroxyl function of ganciclovir until it is removed in the de-protection step. An example for meeting requirement (2) is the second benzyl group protecting the second primary hydroxyl function of ganciclovir which is removed just prior to the esterification step. An example for meeting requirement (3) is the acetyl group, or the trityl or monomethoxytrityl group protecting the amino group of the guanine ring system of ganciclovir, as the unprotected amino group does not interfere with the esterification (step III).

In general, the qualification of potential blocking agents that render them suitable for use in the preparation of the compound of Formula I include:

(1) Their introduction should proceed quantitatively and smoothly without L-valine racemization;

(2) The blocked intermediate must be stable to conditions of the reactions employed until removal of the protecting group is required;

(3) The blocking group must be susceptible of being readily removed under conditions which do not change the chemical nature of the remainder of the molecule or result in racemization of the L-valine component.

Starting Materials

All starting materials (ganciclovir and L-valine) and the protecting and carboxylic-group-activating reagents employed to make the compound of Formula I are known. Also known are various amino-protected L-valine derivatives, such as N-benzyloxycarbonyl-L-valine, BOC-L-valine and FMOC-L-valine, N-formyl-L-valine and N-benzyloxycarbonyl-N-carboxy-L-valine anhydride, which are all commercially available intermediates, or described in the literature, such as N-allyloxycarbonyl-L-valine.

A preferred protected ganciclovir starting material for the preparation of the preferred compound of the invention is N2-acetyl-bis-O-benzyl-ganciclovir (N2-acetyl-2-(2-amino-1,6-dihydro-6-oxo-purin-9-yl)methoxy-1,3-bis(benzyloxy) propane) which is described in U.S. Pat. No. 4,355,032. Other preferred protected ganciclovir starting materials are N^2-trityl-9-[(3-hydroxy-2-propoxy-1-trityloxy)methyl] guanine [N^2-trityl-2-(2-amino-1,6-dihydro-6-oxo-purin-9-yl)methoxy-1-trityloxy-propan-3-ol] N^2-monomethoxytrityl-9-[(3-hydroxy-2-propoxy-1-monomethoxytrityloxy)methyl]- guanine, the preparation of which is described in *J. Pharm. Sci.* 76(2), p.180–184 (1987) which is incorporated herein by reference 2-(2-Amino-1,6-dihydro-6-oxo-purin-9-yl)methyl-1,3-propanediyl bis(L-valinate) which is the starting material for the partial hydrolysis step is described in European Patent publication 0 375 329.

Preparation of the N-Protected Amino Acid

Prior to carrying out Step III (esterification step), the amino group of L-valine must be protected to avoid its interference with the esterification by undersirable amide formation. The following amino-protecting groups are useful: halocarbonates such as (C_6–C_{12}) aryl lower alkyl carbonates (such as the carboboenzyloxy group derived from benzylchlorocarbonate), or biphenylalkyl halo carbonates, or tertiary alkyl halo carbonates, such as tertiary-butylhalocarbonates, in particular tertiary butylchlorocarbonate, or di(lower)alkyldicarbonates, in particular di(t-butyl)dicarbonate, triphenylmethyl halides such as triphenylmethyl chloride, and trifluoroacetic anhydride. The protecting step is carried out by dissolving or suspending L-valine in an alkaline aqueous solution which may include a lower alkanol. The reaction mixture is cooled while the protecting reagent such as the halocarbonate, preferably in an aqueous or lower alkanol solution is added simultaneously in small portions. During this addition, the reaction mixture is kept at 0 to 30°, preferably 0–5° C. for

several hours until it reaches room temperature. The reaction mixture is concentrated to dryness and the residue is partitioned between an organic phase and water. The aqueous layer is acidified and extracted with an organic solvent for the protected amino acid. The organic phase is washed with water followed by brine washings and dried over magnesium sulfate before evaporation to dryness, and the N-protected amino acid isolated and purified by conventional isolation and purification techniques.

Preparation of Mono-L-valine Ganciclovir

Step I: Ganciclovir, with an optionally protected 2-amino group and both primary hydroxyl functions protected is partially de-protected, for example, by hydrogenation to ganciclovir with the 2-amino group retained in protected form and one protected primary hydroxyl function. Suitable amino-protecting groups are lower alkanoyl groups with 2 or 4 carbon atoms, in particular the acetyl or propionyl group. Other suitable amino-protecting groups are the trityl or substituted trityl groups, such as the monomethoxytrityl group, and the 4,4'-dimethoxytrityl group.

Suitable hydroxy-protecting groups are ether-forming groups that can be removed easily after completion of all other reaction steps. These hydroxy-protecting ether groups include the benzyl or the trityl group. These groups may be substituted in the phenyl ring. Other suitable hydroxy-protecting groups include allyl ether, tetrahydropranyl, silyl, trialkylsiyl ethers which can be removed with hydrogen fluoride in a manner known well to those skilled in the art.

The hydrogenation to remove one hydroxy-protecting group is preferably carried out by dissolving the protected ganciclovir in a solvent system that releases hydrogen in the presence of a catalyst such as a palladium compound, in particular palladium hydroxide, by transfer hydrogenation or other conventional hydrogenation procedures. Other suitable hydrogenation catalysts include hydrogenation catalysts in general such as Pd, Pd on carbon and homogeneous hydrogenation catalysts. The solvent system includes a lower alkanol such as methanol or ethanol and cyclohexane. Generally the reaction will be carried out at temperatures between room temperature and the reflux temperature of the solvent system, for example in refluxing ethanol and cyclohexane under an inert atmosphere and under exclusion of oxygen or air, preferably in a nitrogen atmosphere. The catalyst will be recovered by filtration. The filtrate can be reduced in volume by evaporation of excess solvent. The resulting crude reaction mixture generally includes unchanged starting material and 2-amino-protected ganciclovir and one aliphatic hydroxy group protected as the major products. The separation of these two products is usually performed by isolation procedures known in the art, often by chromatographic methods, preferably on silica gel, followed by elution with appropriate eluents such as mixtures of a lower alkanol with a halogenated lower alkane (preferably ethanol and dichloromethane) to give 2-amino-protected ganciclovir with one aliphatic hydroxy group protected.

Step II: Ganciclovir with a protected 2-amino group and one aliphatic hydroxy group protected is subjected to de-protection of the amino group. In this step if the amino-protecting group is a lower alkanoyl group basic conditions (pH between 9 to 14) are employed to remove the protecting group. For example, N2-Acetyl-mono-O-benzyl-ganciclovir is treated with an alkaline reagent such as ammonium hydroxide, sodium or potassium carbonate or sodium or potassium hydroxide until the removal of the acetyl group is complete. In general, this reaction will be conducted in the presence of a suitable solvent such as a lower alkanol. Preferably the starting material is dissolved in methanol and a stoichiometric excess of ammonium hydroxide is added. The reaction temperature is kept between 0 to 50° C., preferably at room temperature. After the reaction is complete (which can be determined by TLC), another solvent may be added to facilitate isolation of the de-protected product, such as ethyl ether which leads to precipitation of the de-acylated product which can be filtered off and isolated using conventional separation methods.

Step III: In this step an activated derivative of amino-protected L-valine of the Formula III is esterified with the protected ganciclovir derivative obtained in Step II. Suitable amino-protecting groups for L-valine are the N-benzyloxycarbonyl group, the phthalyl group, the tertiary butyloxycarbonyl group and the N-(9-fluorenylmethoxycarbonyl) or "FMOC" group.

At least 1 equivalent of the protected amino acid and 1 equivalent of a suitable coupling agent or dehydrating agent, for example 1,3-dicyclo-hexylcarbodiimide or salts of such diimides with basic groups should be employed from the start. Other carbodiimides such as N,N'-carbonyl-diimidazole may also be used. Further useful dehydrating agents are trifluoroacetic anhydride, mixed anhydrides, acid chlorides, 1-benzo-triazolyloxy-tris(dimethylamino) phosphonium hexafluorophosphate, PYBOP, 1-hydroxybenzotriazole, 1-hydroxy-4-azabenzotriazole, 1-hydroxy-7-azabenzotriazole, N-ethyl-N'-ethyl-N-40 -(3-(dimethylamino-propyl)carbodiimide hydrochloride, 3-hydroxy-3,4-dihydro-4-oxo-1,2,3-benzotriazine, O-(benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate, O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate, O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate, O-(1H-benzotriazol-1-yl)-1,1,3,3-bis (tetramethylene)-uronium hexafluorophosphate or O-(7-azabenzotriazol-1-yl)-1,1,3,3-bis(tetramethylene)uronium hexafluorophosphate. A description of these coupling agents by L. A. Capino can be found in *J. Am. Chem. Soc.* 1993, 115, p. 4397–4398. Also useful for this purpose are urethane-protected amino acid N-carboxy anhydrides (UNCA's) which have been described by William D. Fuller et. al., *J. Am. Chem. Soc.* 1990, 112, 7414–7416, which is incorporated herein by reference. In summary, any other reagent that produces an anhydride or another activated derivative of the protected amino acid under mild conditions can be used as the coupling agent.

The amino-protected amino acid is dissolved in an inert solvent such as a halogenated lower alkane, preferably dichloromethane under an inert atmosphere, for example nitrogen, and the coupling agent is added (preferably 1,3-dicyclohexylcarbodiimide). The reaction mixture is stirred at temperature between 0 and 50° C., preferably at about room temperature. The reaction mixture is filtered and the reaction product (the anhydride of dry inert solvent such as dry DMF and placed under nitrogen. A solution of an equivalent amount of the product of Step II in an inert solvent is added to the above solution of the anhydride. The reaction is carried out between 0 and 50° C., preferably at about room temperature over 5 to 90 hours. The reaction product can be isolated and purified using conventional methods, such as chromatography. The product usually will contain unreacted N-protected amino acid which can be removed by treatment of a water-immiscible solution (organic phase) of the product with aqueous alkali such as sodium bicarbonate, sodium carbonate, brine and mixtures thereof. From the organic phase the ganciclovir L-valine ester with the protected aliphatic hydroxy group and the

N-protected amino acid can be isolated and purified using conventional isolation and purification techniques.

Step IV (Final De-protection to Give the Product of Formula I): The two protecting groups of the product of Step III are removed by de-protection reactions, preferably in an acidic medium or solvent, most preferably by hydrogenation. De-protection under acidic conditions is preferred, as this will ensure that the amino group liberated in the de-protection reaction will be protonated, that is that the base of Formula I as it is formed in the de-protection reaction will be captured by an at least stoichiometric amount of acid present. Isolating the compound of Formula I as an acid addition salt will protect the desired stereoconfiguration of the compound of Formula I. Therefore, those examples given below that show the de-protection step (a) also show the concomitant salt formation step (b).

The de-protection reaction is carried by dissolving the product of the esterification step in an inert solvent, preferably in an acidic solvent, using an hydrogenation catalyst, such as palladium on carbon, platinum, using elevated hydrogen pressure between 1 and 2000 psi, preferably 20 to 200 psi. The completion of the reaction can be monitored using conventional TLC analysis. The hydrogenation is continued until the conversion is complete, if required with addition of further hydrogenation catalyst. The catalyst is removed and washed. The combined filtrates from filtration and the washings are concentrated and lyophilized to isolate ganciclovir L-valine ester. The purification of the product and the isolation of a crystalline ester is carried out by recrystallization or other purification techniques, such as liquid chromatographic techniques.

If the tertiary butyloxycarbonyl group is being used as amino-protecting group, its removal is effected with acid, such as HCl and isopropanol as a solvent or with trifluoroacetic acid neat.

Alternatively if the esterification step has been carried out with a trityl or substituted trityl-protected ganciclovir derivative such protecting groups can be removed by treatment with an aqueous alkanoic acid or trifluoroacetic or hydrochloric acid at temperature between −2020 C. and 100° C., for example aqueous acetic acid.

Allyl groups are removed by isomerization to the vinyl ethers with rhodium or palladium catalysts, followed by acidic aqueous hydrolysis.

Other Methods of Preparation [Steps (b), (d), and (e)]

One of ordinary skill in the art will also recognize that the compound of Formula I may be prepared as an acid addition salt or as the corresponding free base. If prepared as an acid addition salt, the compound can be converted to the free base by treatment with a suitable base such as ammonium hydroxide solution, sodium hydroxide, potassium hydroxide or the like. However, it is important to point out that the free base of Formula I is more difficult to characterize than its acid addition salts. When converting the free base to an acid addition salt, the compound is reacted with a suitable organic or inorganic acid (described earlier). These reactions are effected by treatment with an at least stoichiometric amount of an appropriate acid (in case of the preparation of an acid addition salt) or base (in case of liberation of the free compound of Formula I). In the salt-forming step of this invention typically, the free base is dissolved in a polar solvent such as water or a lower alkanol (preferably isopropanol) and mixtures thereof and the acid is added in the required amount in water or in lower alkanol. The reaction temperature is usually kept at about 0 to 50° C., preferably at about room temperature. The corresponding salt precipitates spontaneously or can be brought out of the solution by the addition of a less polar solvent, removal of the solvent by evaporation or in a vacuum, or by cooling the solution.

The reaction conditions of condensation step (d) are described in European Patent Publication 187 297. This condensation step is one of the preferred methods for the preparation of the diastereomers of the monoester. In this condensation step guanine, preferably with a protected 2-amino group is reacted with a glycerol derivative. The glycerol derivative, such as a 1-halo-3-benzyloxy-2-acyloxymethoxyglycerol, is reacted with guanine or a substituted guanine derivative in an aprotic hydrocarbon solvent (such as benzene or toluene, or xylenes) or DMF with a hexa-lower alkyl silazane, for example, hexamethylsilazane, hexaethylsilazane, or the like, and a catalyst at temperatures between 30° C. and reflux temperature. The catalyst is a Lewis acid salt, such as trialkyl silyl salt, such as the sulfate or a trifluoroalkyl sulfonate, a chlorosilane, or ammonium sulfate and pyridine. For a more detailed disclosure of the reaction conditions for condensation step (d) see the disclosure of European Patent Publication 187 297 which is incorporated by reference herein. In general, Y^1 and Y^2 need to be chosen in such a way as to permit the obtention of the mono-L-valine ester of Formula I. Y^1 can be an amino-protected L-valinyl group, or a group convertible to the L-valinyl group.

The compound of this invention may also be prepared from 2-(2-amino-1,6-dihydro-6-oxo-purin-9-yl)methoxy-1,3-propanediyl bis(L-valinate) which is described in European Patent publication 0 375 329. The conversion to 2-(2-amino-1,6-dihydro-6-oxo-purin-9yl)methyoxy-3-hydroxy-1-propanyl-L-valinate is effected by partial hydrolysis [Step (e)] of one L-valine ester group under controlled conditions which result in the preferential cleavage of only one amino acid acyl residue. A salt of 2-(2-amino-1,6-dihydro-6-oxo-9H-purin-9-yl)methoxy-1,3-propanediyl bis-L-valinate, preferably as the bis acetate salt, is dissolved in de-ionized water, and partially neutralized with weak base, such as a dilute ammonium hydroxide solution. The mixture will is kept at room temperature for one to several days, preferably 48 to 72 hrs.

Alternatively, enzymatic hydrolysis with an esterase, such as porcine esterase or a peptidase, such as a carboxypeptidase can also be used to effect partial hydrolysis.

The monoester can be separated from the bis ester by preparative chromatography under weak acidic conditions (pH 3 to 5, preferably pH 4). The solvent used for chromatographic separation will be removed and 2-(2-amino-1,6-dihydro-6-oxo9H-purin-9-yl)-methoxy-3-hydroxy-1-propanyl L-valinate salt will be isolated as a mixture of two diastereomers.

Isolation of Stereoisomers

From the Formula (I) it is apparent that the compound of the invention has one asymmetric carbon atom (chiral center) in the propanyl chain, in addition to the asymmetric carbon atom in L-valine. Therefore, two diastereomeric forms exist, the (R)- and (S)- form as determined by the rules of Cahn et al.

A number of methods suitable for the separation of the diastereomers can be used but the preferred methods use techniques that take advantage of the different physical properties of the two diastereomers. In general, the diastereomers are separated by chromatography but preferred are separation/resolution techniques depending on differences in solubility, such as fractional crystallization.

Specifics of the separation techniques applicable to the preparation of diastereomers of the Formula I are described

in Jean Jacques, André Collet, Samuel H. Wilen, *Enantiomers, Racemates and Resolutions,* John Wiley & Sons, Inc. (1981), which is incorporated herein by reference.

Alternatively, the compound of the invention may be prepared using optically active reactants. When pure diastereomers of mono-L-valine ganciclovir are prepared the condensation step (d) is the preferred method of synthesis. However, if optically active reagents are being used it would be important to avoid the pH range above 6, as at the higher pH range interconversion of the free compound of Formula I occurs. For example, at pH 7 and 40° C. the diastereomeric mixtures of Formula I have a half-life of less than one hour.

The stereoconfiguration at the second chiral center of the compound of Formula I can be assigned by circular dichroism, preferably by Single Crystal X-Ray Analysis of a heavy atom derivative, or correlation with material prepared by total synthesis from a single glycerol enantiomer of known configuration.

The Manufacture of Crystalline 2-(2-Amino-1,6-dihydro-6-oxo-purin-9-yl)methoxy-3-hydroxy-1-propanyl-L-valinate

The compound of the invention can be, and has been, produced in crystalline form. This is a decisive advantage over the compounds disclosed in the prior art which have been described as non-crystalline materials. The advantage resides in the fact that pharmaceutical formulations can be more easily produced with a crystalline material. A crystalline material can be processed efficiently and is suspectible of being more reproducibly characterized than a non-crystalline material, and the quality of the crystalline materials of the invention can be much more readily ascertained than that of non-crystalline materials.

In order to produce crystalline material it is preferred to use a salt of 2-(2-amino-1,6-dihydro-6-oxo-purin-9yl) methoxy-3-hydroxy-1-propanyl L-valinate. Preferred crystalline salts are the acetate and the hydrochloride salt. It is preferred to initiate crystallization of the salt by dissolving the hydrochloride or acetate salt in water and adding an organic solvent miscible with water such as methanol, ethanol, isopropanol, tetrahydrofuran or acetonitrile. Alternatively, the hydrochloride salt can be crystallized from an anhydrous lower alkanol solution, such as methanol, ethanol, by the addition of other organic solvents such as ethyl acetate, isopropanol, tetrahydrofuran or toluene.

The following preparations and examples are given to enable those skilled in the art to more clearly understand and to practice the present invention. They should not be considered as limiting the scope of the invention, but merely as being illustrative and representative thereof.

EXAMPLE 1

Preparation of (S)-2-(2-Amino-1,6-dihydro-6-oxo-purin-9-yl)methoxy-3-benzyloxy-propan-1-ol

A. (R)-(1-Chloro-2-acetoxymethoxy-3-benzyloxy)propane

HCl gas (dried by passing through concentrated H_2SO_4) was bubbled into a stirred mixture of (S)-(+)-benzyloxymethyloxirane (500 mg, 3.06 mmol) and paraformaldehyde (201 mg, 6.71 mmol) in dichloromethane (8 mL) at 0° C. until all the solid dissolved (ca. 45 min). The resulting solution was stored at 0° C. for 16 hours. After drying with magnesium sulfate, the solvent was evaporated to provide (R)-(1-chloro-2-chloromethoxy-3-benzyloxy) propane. This chloromethyl ether intermediate was dissolved in acetone (3 mL) and added dropwise to a mixture of potassium acetate (2.1 g, 21.4 mmol) in acetone (7 mL). The mixture was stirred at ambient temperature for 16 hours. The solid was filtered off and the filtrate concentrated. The residue was taken up in 20 mL of toluene and the washed with saturated sodium bicarbonate solution (10 mL) and water (2x20 mL). The organic layer was dried over sodium sulfate. After filtration, the filtrate was concentrated and the residue purified by flash chromatography over silica gel (hexane/ethyl acetate=7/1) to provide (R)-(1-chloro-2-acetoxymethoxy-3-benzyloxy)propane (810 mg, 2.97 mmol) as a colorless oil in 97% yield (the isomeric ratio was 12:1).

B. (R) 2-(2-Amino-1,6-dihydro-6-oxo-purin-9-yl)methoxy-1-chloro-3-benzyloxy-propane

A solution of persilylated guanine (1.09 g, 2.95 mmol) in DMF (3.2 mL) was added to 81- mg of (R)-(1-chloro-2-acetoxymethoxy-3-benzyloxy)propane. The solution was stirred at 130° C. for 1 hour before trimethylsilyl trifluoromethanesulfonate was introduced. Stirring was continued at the same temperature for 4 hours. The mixture was cooled to room temperature and partitioned between water and ethyl acetate. The aqueous layer was extracted exhaustively with ethyl acetate. The combined organic layer was dried over magnesium sulfate, filtered and concentrated. The residue was purified by chromatography over silica gel to provide (R) 2-(2-amino-1,6-dihydro-6-oxo-purin-9-yl) methoxy-1-chloro-3-benzyloxy-propane along with its N-7 isomer. The ratio of N-9 to N-7 isomer was about 2.3:1.

C. (R)-2-(2-amino-1,6-dihydro-6-oxo-purin-9-yl)methoxy-1-acetoxy-3-benzyloxy-propane

A mixture of the product from the previous step, potassium acetate, (large excess) and DMF was heated to reflux for 5 hours. The resulting brown mixture was cooled to room temperature and filtered through a plug of Celite. The filter bed was rinsed with methanol. The filtrate was evaporated and residual DMF removed in vacuo. The crude product was purified by flash chromatography over silica gel (CH_2Cl_2-methanol:10:1) to provide (R)-2-(2-amino-1,6-dihydro-6-oxo-purin-9-yl)methoxy-1-acetoxy-3-benzyloxy-propane as a pale yellow solid.

D. (S)-2-(2-Amino-1,6-dihydro-6-oxo-purin-9-yl)methoxy-1-benzyloxy-propan-3-ol

A mixture of (R)-2-(2-amino-1,6-dihydro-6-oxo-purin-9-yl)methoxy-1-acetoxy-3-benzyloxy-propane in 30% ammonia / methanol (1:2) was stirred at ambient temperature for 18 hours. The solvent was evaporated and the residue was triturated with a small amount of methanol. The pale yello solid was collected to give (S)-2-(2-Amino-1,6-dihydro-6-oxo-purin-9-yl)methoxy-1-benzyloxy-propan-3-ol. The mother liquor was concentrated and the residue recrystallized from hot methanol to give a second crop of the product.

EXAMPLE 2

Preparation of 2-(2-Amino-1,6-dihydro-6-oxo-purin-9-yl)methoxy-1-benyzloxy-propan-3-ol

A. N2-Acetyl-2-(2-amino-1,6-dihydro-6-oxo-purin-9-yl) methoxy-1,3-bis(benzyloxy)propane, 54.2 g (114 mmol) was dissolved in refluxing ethanol (815 mL) and cyclohexane (610 mL) was added under a nitrogen atmosphere. A slurry of palladium hydroxide (16 g) in ethanol (50 mL) was added to the reaction mixture and the mixture was refluxed under nitrogen for 1.5 hrs. The hot mixture was filtered through Celite and the filtrate was concentrated on a rotary evaporator. The resulting crude reaction mixture was chromatographed on silica gel. Elution with 8% methanol/92% dichloromethane followed by 10% methanol/90% dichloromethane results in N2-acetyl-2-(2-amino-1,6-dihydro-6-oxo-purin-9-yl)methoxy-1,3-bis(benzyloxy)propane (starting material) (18.6 g, 16%) and N2-acetyl-2-(2-amino-1,6-dihydro-6-oxo-purin-9-yl)methoxy-1-benzyloxy-propan-3-ol, (17.6 g, 40%).

B. N2-Acetyl-2-(2-amino-1,6-dihydro-6-oxo-purin-9-yl) methoxy-1-benzyloxy-propan-3-ol, 21.9 g (56.5 mmol), was dissolved in methanol (200 mL) and ammonium hydroxide (101 mL) was added. The mixture was stirred over night at room temperature. Ethyl ether (400 mL) was added to the white slurry and the mixture was filtered. The precipitate was washed consecutively with ethyl ether (100 mL), water (100 mL) and ethyl ether (100 mL) and dried under high vacuum over night resulting in 15.9 g (46.13 mmol, 82%) of 2-(2-amino-1,6-dihydro-6-oxo-purin-9yl)methoxy-1-benzyloxy-propan-3-ol. Evaporation of the filtrate and suspension of the resulting precipitate in ethyl ether (200 mL) followed by filtration and drying under high vacuum results in an additional 2.3 g (6.7 mmol, 12%) of the product.

Analysis Calcd. for $C_{16}H_{19}N_5O_4$ (345.36): C, 55.65; H, 5.55; N, 20.28. Found: C, 55.25; H, 5.60; N, 20.12.

EXAMPLE 3

Preparation of 2-(2-Amino-1,6-dihydro-6-oxo-purin-9-yl)methoxy-3-hydroxy-1-propanyl-L-valinate

A. 2-((2-Amino-1,6-dihydro-1,6-dihydro-6-oxo-purin-9-yl)methoxy)-3-benzyloxy-1-propanyl N-(benzyloxycarbonyl)-L-valinate N-Benzyloxycarbonyl-L-valine, 43.66 g (0.174 mol, 3 equivalents), was suspended in dichloromethane, 72 mL, and 1,3-dicyclohexylcarbodiimide, 14.34 g (69.5 mmol, 1.2 equivalents), was added. The mixture was stirred under nitrogen for 48 hrs. The mixture was filtered through a glass fritte and the white solid residue was washed with dichloromethane, 75 mL. The combined filtrate was stirred under nitrogen and a suspension of 2-(2-amino-1,6-dihydro-6-oxo-purin-9-yl)methoxy-3-benzyloxy-propan-1-ol, 20 g (57.91 mmol, 1 equivalents) in dimethylformamide, 90 mL, was added followed by 4-dimethylaminopyridine, 1.77 g (14.4 mmol, 0.25 equivalents). The mixture was stirred under nitrogen for 18 hours, poured into water 1200 mL, and extracted with a mixture of ethyl acetate (350 mL) and toluene (350 mL). The aqueous layer was separated and the organic layer was washed with half saturated sodium biocarbonate, 600 mL, followed by water (200 mL). The organic layer was dried over magnesium sulfate and concentrated under reduced pressure. The residue was precipated from a mixture of ethyl acetate and cyclohexane to give 2-((2-amino-1,6-dihydro-6-oxo-purin-9-yl)methoxy)-3-benzyloxy-1-propanyl N-(benzyloxycarbonyl)-L-valinate as an amorphous solid.

B. 2-(2-Amino-1,6-dihydro-6-oxo-purin-9-yl)methoxy-3-hydroxy-1-propanyl-L-valinate hydrochloride 2-(2-Amino-1,6-dihydro-6-oxo-purin-9-yl)methoxy)-3-benzyloxy-1-propanyl N-(benzyloxycarbonyl)-L-valinate, 224.8 g (0.39 mol), was dissolved in methanol, 1.2 L, and concentrated hydrocholoric acid, 32.4 mL (0.39 mol), was added dropwise. The mixture was placed under nitrogen and palladium on carbon, 67.4 g, was added. The mixture was hydrogenated in a Parr bomb under hydrogen (40 –100 psi, average 80 psi pressure) for 48 hours. 5 g additional palladium on carbon was added, and the mixture was hydrogenated at 100 psi for 24 hours. The mixture was filtered through a pad of Celite and the residue was washed with methanol, 1 L. The filtrate was evaporated to dryness under reduced pressure. The residue was dissolved in water, 150 mL, and heated to 60° C. Isopropanol (830 mL) was slowly added dropwise with stirring while maintaining the temperature (60–70°C.). The solution was slowly cooled to ambient temperature over 16 hours. The resulting crystalline solution was heated to 30° C. and additional isopropanol added, 220 mL. The mixture was allowed to slowly cool to a final temperature of −11° C. over 4 hours. The crystals were isolated by filtration and washed with 200 mL of cold 2% water/isopropanol to obtain 2-(2-amino-1,6-dihydro-6-oxo-purin-9-yl)methoxy-3-hydroxy-1-propanyl-L-valinate hydrochloride (120.5 g, 79% yield). The compound undergoes a phase change at 142° C. and decomposes at 175° C.

EXAMPLE 4

Preparation of Crystalline 2-(2-Amino-1,6-dihydro-6-oxo-purin-9-yl)methoxy-3-hydroxy-1-propanl-L-valinate Salt

2-(2-Amino-1,6-dihydro-6-oxo-purin-9-yl)methoxy-3-hydroxy-1-propanyl-L-valinate hydrochloride, 150 g, was dissolved in water, 150 mL, and heated to 50–60° C. Isopropanol (830 mL) was slowly added dropwise with stirring while slightly increasing the temperature to 60–70° C. The solution was slowly cooled to 25° C. over 20 hours. The resulting crystalline solution was heated to 30° C. and additional isopropanol added, 220 mL. The mixture was allowed to slowly cool to a final temperature of −11° C. over 6 hours. The crystals were isolated by filtration and washed with 200 mL of cold 2% water/isopropanol to obtain 2-(2-amino-1,6-dihydro-6-oxo-purin-9-yl)methoxy-3-hydroxy-1-propanyl-L-valinate hydrochloride crystals (135 g, 90% yield). The compound undergoes a phase change at 142° C. and decomposes at above 175° C.

In a similar manner 2-(2-amino-1,6-dihydro-6-oxo-purin-9-yl)methoxy-3-hydroxy-1-propanyl-L-valinate acetate may be prepared in crystalline form.

EXAMPLE 5

Preparation of (S)-2-(2-Amino-1,6-dihydro-6-oxo-purin-9yl)methoxy-3-hydroxy-1-propanyl-L-valinate hydrochloride

A. (S)-2-(2-Amino-1,6-dihydro-6-oxo-purin-9-yl) methoxy)-3-benzyloxy-1-propanyl N-(benzyloxycarbonyl)-L-valinate N-Benzyloxycarbonyl-L-valinate, 437 mg (1.74 mmol; 3 equivalents), is suspended in dichloromethane, 1mL, and 1,3-dicyclohexylcarbodiimide, 143 mg (0.7 mmol, 1,2 equivalents), is added. The mixture is stirred under nitrogen for 48 hours. The mixture is filtered through a glass fritte and the white solid residue washed with dichloromethane, 1 mL. The combined filtrate is stirred under nitrogen and a suspension of (R)-2-(2-amino-1,6-dihydro-6-oxo-purin-9-yl)methoxy-3-benzyloxy-propan-1-ol, 200 mg (0.58 mmol, 1 equivalent) in dimethylformamide, 1.5 mL, is added followed by 4-dimethylaminopyridine, 18 mg (14.4 mmol, 0.25 equivalents). The mixture is stirred under nitrogen for 18 hours, poured into water, 12 mL, and extracted with a mixture of ethyl acetate (3.5 mL) and toluene (3.5 mL). The aqueous layer is separated and the organic layer washed with half saturated sodium bicarbonate, 6 mL, followed by water (2 mL). The organic layer is dried over magnesium sulfate and concentrated under reduced pressure. The residue is precipitated from a mixture of ethyl acetate and cyclohexane to give (S)-2-(2-amino-1,6-dihydro-6-oxo-purin-9-yl) methoxy)-3-benzyloxy-1-propanyl N-(benzyloxycarbonyl)-L-valinate as a solid.

B. (S)-2-(2-Amino-1,6-dihydro-6-oxo-purin-9-yl) methoxy-3-hydroxy-1-propanyl-L-valinate hydrochloride (S)-2-(2-Amino-1,6-oxo-purin-9-yl)methoxy)-3-benzyloxy-

1-propanyl N-(benzyloxycarbonyl)-L-valinate, 225 mg (3.9 mol), is dissolved in methanol, 12 mL, and concentrated hydrochloric acid, 0.3 mL (3.9 mmol), is added. The mixture is placed under nitrogen and palladium on carbon, 674 mg, is added. The mixture is hydrogenated in a Parr bomb under hydrogen (40–100 psi, average 80 psi pressure) for 48 hours. 50 mg additional palladium on carbon are added, and the mixture hydrogenated at 100 psi for 24 hours. The mixture is filtered through a pad of Celite and the residue is washed with methanol, 10 mL. The filtrate is evaporated to dryness under reduced pressure. The residue is dissolved in water 1.5 mL, and heated to 60° C. Isopropanol (8 mL) is slowly added with stirring while maintaining the temperature (60–70° C.). The solution is slowly cooled to ambient temperature over 16 hours. The resulting solution is heated to 30° C. and additional isopropanol added, 2 mL. The mixture is allowed to slowly cool to a final temperature of −11° C. over 4 hours. The crystals are isolated by filtration and washed with 2 mL of cold 2% water/isopropanol to obtain (S)-2-(2-amino-1,6-dihydro-6-oxo-purin-9yl) methoxy-3-hydroxy-1-propanyl-L-valinate hydrochloride.

EXAMPLE 6

Preparation of 2-(2-Amino-1,6-dihydro-6-oxo-purin-9-yl)methoxy-3-hydroxy-1-propanyl-L-valinate acetate from 2-(2-Amino-1,6-dihydro-6-oxo-purin-9-yl)methoxy-1,3-propanediyl bis (L-valinate) bis acetate

2-((2-Amino-1,6-dihydro-6-oxo-9H-purin-9-yl)methoxy)-1,3-propanediyl bis-L-valinate bis acetic acid salt, 100 mg (lyophilized sample contained 0.6 equivalents of excess acetic acid, 0.164 mmol (=a total of 0.426 mmol of acetic acid) was dissolved in de-ionized water, 0.4 mL, and partially neutralized by the addition of 24 mL of a 0.015M ammonium hydroxide solution (=0.36 mmol). The mixture was left at room temperature for 67 hrs. The sample was injected in two equal lots onto a preparative reverse phase HPLC column (YMC-Pack, ODS-AM DM-33.5, 2×250 mm; YMC Inc.). Separation was achieved with a solvent system of 10% methanol /90% 0.1M ammonium acetate buffered to pH 4 with acetic acid, flow rate: 9.5 mL/min and the detector set to 256 nm. The two peaks representing the two diastereomers of the mono ester product were collected. The solvent was removed under high vacuum to about 2 mL and the residue was lyophilized twice from water containing acetic acid (0.1%) to remove the buffer. 45 mg (0.112 mmol=68%) of 2-((2-amino-1,6-dihydro-6-oxo-9H-purin-9-yl)ethoxy)-3-hydroxy-1-propanyl L-valinate acetic acid salt was isolated as a mixture of two diastereomers with the following characteristic peaks of the NMR spectrum: ^{1}H NMR (300 Mhz) DMSO-d_6 solution: δ 7.78 (1 H, s, H C-8), 6.48 and 6.45 (2 br.s., 2 H, NH_2), 5.44 (mAB, J=11 Hz) and 5.43 (s) total of 2 H, CH2; 1.91 (s, 3 H, CH_3COO^-), 0.83+0.82 (2 d, J=7 Hz, 3 H, CH_3), 0.75+0.76 (2 d, J=7 Hz, 3 H, CH_3).

EXAMPLE 7

Separation of (R,S) 2-(2-amino-1,6-dihydro-6-oxo-purin-9-yl)methoxy-3-hydroxy-1-propanyl-L-valinate

A solution of (R,S) 2-(2-amino-1,6-dihydro-6-oxo-purin-9-yl)methoxy-3-hydroxy-1-propanyl-L-valinate (1.66 g) in 90% 0.1M ammonium acetate, acidified to pH 4 with acetic acid, 10% methanol (9.6 mL) was applied to a YMC-Pack ODS-AM HPLC column (cat. no. DM-33-5; size, 250×20 mmI.D.; particle, S-5 mm, 120 A) in 48 injections of 200 μL with elution at 9.5 mL/min. using a mobile phase of 90% 0.1M ammonium acetate acidified to pH 4 with acetic acid, 10% methanol. The peaks were detected using Knauer Variable Wavelength Monitor set to 256 nm and the fractions collected manually. Three sets of fractions were collected, peak 1 (retention time 24.4 min.), an overlapping region between the peaks and peak 2 (retention time 27.8 min.). The fractions of each set were combined, evaporated under reduced pressure to remove the methanol then lyophilized to remove the remaining volatile components. The residue was dissolved in water, acidified to pH 4 with acetic acid and lyophilized again yielding peak 1 (1.57 g) and peak 2 (0.91 g). HPLC analysis of the products using a YMC-Pack ODS-AM Column (cat. no. RM-33-5; size, 250×4.6 mmI.D.; particle, S-5 mm, 120 A) with elution at 0.5 mL/min. using a mobile phase of 90% 0.1M ammonium acetate, acidified to pH 4 with acetic acid, 10% methanol indicated that peak 1 (retention time 24.4 min. on the preparative column) contained a mixture 70% peak 1 (retention time 21.1 min.). 26.4% peak 2 (retention time 24.6 min.) and 2.8% fully hydrolyzed product (retention time 12.4 min.); and peak 3 (retention time 27.8 min. on the preparative column) contained a mixture 68.5% peak 2 (retention time 22.0 min.), 27.5% peak 1 (retention time 20.2 min.) and 4% fully hydrolyzed product (retention time 11.6 min.). Peak 2 (0.91 g) and peak 1 (1.57 g) were each dissolved in 90% 0.1M ammonium acetate acidified to pH 4 with acetic acid, 10% methanol (3.60 mL) and purified again using the system outlined before in of 18 injections of 200 mL. Two sets of fractions corresponding to peaks 1 and 2 were collected, combined, partially evaporated under reduced pressure to remove the methanol and the remainder lyophilized to remove the remaining volatile components. The residue from each set of fractions was dissolved in water, carefully acidified to pH 4 with acetic acid and lyophilized once more. The fractions corresponding to peak 1 yielded a white fluffy solid (0.70 g) which appeared hygroscopic on exposure to air; HPLC analysis (performed as outlined before) indicated this to be a mixture containing 94.9% peak 1 (retention time 21.1 min.) 4.6% peak 2 (retention time 26.7 min.) and 0.5% fully hydrolyzed product (retention time 11.8 min.); ^{1}H NMR analysis (^{66}DMSO, δ values quoted relative to tetramethylsilane as internal standard) showed characteristic peaks δ 5.43 (m_{AB}, 2 H, J_{AB}=11.1 Hz, d_A 5.44, d_B 5.43), 3.02 (d, 1 H, J=5.2 Hz), 0.82 (d, 3 H, J=6.8 Hz), 0.75 (d, 3 H, J=6.8 Hz). The fractions corresponding to peak 2 yielded a white fluffy solid (0.81 g) which appeared hygroscopic on exposure to air; HPLC analysis (performed as outlined before) indicated this to be a mixture containing 91.0% peak 2 (retention time 29.8 min.) 8.4% peak 1 (retention time 28.4 min.) and 0.6% fully hydrolyzed product (retention time 14.4 min.); ^{1}H NMR analysis (^{66}DMSO, δ values quoted relative to tetramethylsilane as internal standard) showed characteristic peaks d 5.43 (s, 2 H), 2.99 (d, 1 H, J=5.2 Hz), 0.83 (d, 3 H, J=6.8 Hz), 0.76 (d, 3 H, J=6.8 Hz).

EXAMPLE 8

A. Preparation of (R) 2-(2-amino-1,6-dihydro-6-oxo-purin-9-yl)methoxy-3-benzyloxy-1-propanyl (N-benzyloxycarbonyl)-L-valinate

To a solution of N-benzyloxycarbonyl-L-valine (327 mg, 1.30 mmol, 3 equivalents) in dichloromethane (25 mL) under nitrogen was added 1,3-dicyclo-hexylcarbodiimide (134 mg, 0.65 mmol, 1.5 equivalents) and the reaction mixture stirred at room temperature for 13.5 hours. The

resulting mixture was filtered to remove the insoluble material and the solvent evaporated under reduced pressure using a rotary evaporator. The resulting white foam was dissolved in dry DMF (10 mL) added directly to a solution of (S)-2-(2-amino-1,6-dihydro-6-oxo-purin-9-yl)methoxy-3-benzyloxy-1-propan-1-ol (150 mg, 0.43 mmol, 1 equivalent) also in dry DMF (10 mL). 4.4-Dimethylamino-pyridine (13 mg, 0.11 mmol, 0.25 equivalents) was added to the DMF solution and the reaction mixture left to stir at room temperature for 27 hours at which point TLC analysis indicated consumption of the starting materials. The reaction mixture was evaporated under reduced pressure and the crude product purified by flash chromatography using a mobile phase of 95% methylene chloride, 5% methanol to yield the title compound as an amorphous solid (158 mg, 63%).

B. Preparation of (R)-2-(2-amino-1,6-dihydro-6-oxo-purin-9-yl)methoxy-3-hydroxy-1-propanyl-L-valinate hydrochloride

(R)-2-(2-amino-1,6-dihydro-6-oxo-purin-9-yl)methoxy-3-benzyloxy-1-propanyl (N-benzyloxy-carbonyl)-L-valinate (158 mg, 0.27 mmol) was dissolved in methanol (15 mL) and concentrated hydrochloric acid (24 mL, 0.27 mmol) added. The mixture was placed under nitrogen and 10% palladium on carbon (48 mg) was added. The mixture was hydrogenated in a Parr shaker under hydrogen (50 psi of pressure) for 5 hours. The mixture was filtered through a pad of Celite and the residue washed with methanol (25 mL). Evaporation of the combined filtrate and washings under reduced pressure yielded the title compound (107 mg, 95%). HPLC analysis of the product using a YMC-Pack ODS-AM column (cat. no. RM-33-5; size, 250×4.6 mmI.D.; particle, S-5 mm, 120 A) with elution at 0.5 mL/min. using a mobile phase of 90% 0.1M ammonium acetate acidified to pH 4 with acetic acid, 10% methanol indicated it to be a 85:15 mixture of (R) and (S) diastereomers.

EXAMPLE 9

Determination of Oral Absorption (Bioavailability) in the Rat

The following assay was used to determine the oral absorption (oral bioavailability) of the compound of Formula I (L-monovaline ester of ganciclovir) and of other ganciclovir amino acid esters, other ganciclovir esters and ethers examined for comparative purposes.

To measure the oral bioavailability of a compound first the plasma level of the compound in male rats was determined after a single oral (p.o.) dose of the compound. To measure the oral bioavailability of a pro-drug, first the plasma level of the active compound, in this case ganciclovir, was determined in male rats after a single po dose of the pro-drug. Then the plasma level of the active compound, ganciclovir, is determined in male rats after a single intravenous (iv) dose of the compound. For ganciclovir the single dose in each case, po and iv, is 10 mg/kg; for a prodrug ester (including the L-monovaline ester of ganciclovir) the single dose in each case, oral and iv, is a dose equimolar to 10 mg/kg of ganciclovir. From the two measurements following p.o. and iv administration, the oral bioavalability of a compound was calculated by dividing the total area under the concentration vs. time curve following p.o. administration by the total area under the concentration vs. time curve following iv administration, appropriately corrected for dose, according to the equation:

$$F_{(p.o.)}(\%)=[AUC_{(p.o.)}/AUC_{(i.v.)}]\times[Dose_{(i.v.)}/Dose_{(p.o.)}]\times 100$$

The AUC (total area under the curve) values were calculated over the entire time range which was analyzed from 0–24 hr.

The dose vehicle for oral and intravenous dosing consisted normal saline containing 2% acetic acid. In both cases the compound concentration was equivalent to 4.0 mg/mL ganciclovir with a dose rate equivalent to 10 mg/kg (2.5 mL/kg) of ganciclovir. A 200 gm rat received 0.5 mL of the oral drug solution by gavage or via injection into the tail vein.

The rats were acclimatized to the laboratory environment for three days and fasted overnight before start of the experiment and until 4 hours after dosing. Blood was collected from 4 rats at each of the following times: 0 min (pre-dose), 5 min (iv only), 15 min, 30 min, 1 hr, 2 hr, 3 hr, 5 hr. 7 hr 10 hr and 24 hr. The blood was immediately centrifuged to obtain the plasma and the plasma frozen at −20 ° C. until analysis.

Assay of Ganciclovir in Plasma

Aliquots of plasma (0.50 mL) were mixed with 0.020 mL of internal standard (acyclovir 15 μg/mL in 10% methanol/water) and 3.0 mL of acetonitrile. The mixture was vortexed and the resulting precipitate was removed by centrifugation (4,000 g, 10 min). The supernatant was evaporated to dryness under nitrogen and reconstituted in 200 μL of HPLC mobile phase. Aliquots (0.05 mL) were analyzed by HPLC using a Keystone Hypersil BDS, 250×4.6 mm C 18 column. The mobile phase contained 2% acetonitrile in 30 mM sodium phosphate buffer containing 5 mM heptane sulfonic acid, pH 2.0 and was pumped at 1.0 mL/min. Ganciclovir and internal standard were detected and measured by UV absorbance at 254 nm.

ORAL BIOAVAILABILITY

COMPOUND	ORAL BIO-AVAILABILITY (F %)	REFERENCE
Ganciclovir (G) {2-(2-Amino-1,6-dihydro-6-oxo-purin-9-yl)-methoxy-1,3-propanediol}	7.9	US 4,355,032
G-bis(propionic acid) ester	17.7	J. Pharm Sci. 76, p. 180–184 (1987)
G-bis (L-valine) ester	52.0	EP 0 375 329
G-L-valine ester benzyl ether	non-detectable	—
G-bis(phenylglycine) ester diacetate	8.18	
G-dibenzyl ether	non-detectable	
Amino Acid Ester of the Invention		
G-L-valinate acetate	84.0	
G-L-valinate hydrochloride	98.1	

EXAMPLE 10

Determination of Oral Absorption (Bioavailability) in the Cynomolgus Monkey

The following assay was used to determine the oral absorption (oral bioavailability) of the compound of Formula I in the Cynomolgus Monkey.

Animals, Dosing and Sample Collection

Male cynomolgus monkeys weighing 5 to 7 kilos were used. The animals were fed monkey chow, fruit and water and maintained on a 12 hour light cycle. The tested compounds were formulated at a concentration equimolar to a 10 mg/mL solution of ganciclovir in saline. The oral formulation was administered by gavage at a rate of 1.0 mL/kg for a final dose equimolar to a 10 mg/kg dose of ganciclovir. The

iv formulation of ganciclovir was formulated in saline containing 0.2% HCl at a concentration of 20 mg/mL and administered at a rate of 0.5 mL/kg.

The animals were fasted beginning the evenging prior to dosing and until 4 hr after dosing. Blood samples were taken from each monkey at 0 (predose), 5 min (iv only), 15 min, 30 min, 1 hr, 2 hr, 3 hr, 5 hr, 7 hr, 10 hr and 24 hr after dosing. The blood samples were collected in heparinized syringes and the plasma was immediately isolated by centrifugation and frozen at −20° C. until analysis.

Assay of Ganciclovir in Plasma

Aliquots of plasma (0.50 mL) were mixed with 0.020 mL of internal standard (acyclovir, 15 μg/mL in 10% methanol/water) and 3.0 mL of acetonitrile. The mixture was vortexed and the resulting precipitate was removed by centrifugation (4,000 g, 10 min). The supernatant was evaporated to dryness under nitrogen and reconstituted in 200 μL of HPLC mobile phase. Aliquots (0.05 mL) were analyzed by HPLC using a Keystone Hypersil BDS, 250×4.6 mm C 18 column. The mobile phase contained 2% acetonitrile in 30 mM sodium phosphate buffer containing 5 mM heptane sulfonic acid, pH 2.0 and was pumped at 1.0 mL/min. Ganciclovir and internal standard were detected and measured by UV absorbance at 254 nm.

The bioavailability (F) is calculated according to the equation given in Example 9.

The prodrug 2-(2-amino-1,6-dihydro-6-oxo-purin-9-yl) methoxy-3-hydroxy-1-propanyl-L-valinate had an oral bioavailability of 35.7%. 2-(2-Amino-6-dihydro-6-oxo-purin-9-yl)methoxy-1,3-propanediyl bis (L-valinate) had an oral bioavailability of 23.5%. Ganciclovir has a bioavailability of 9.9%. Giving the same prodrug orally and ganciclovir iv to the same monkeys results in a mean oral bioavailability for the prodrug of 41.6%.

EXAMPLE 11

The following examples of the proposed ganciclovir L-valine monoester capsules contain as excipients povidone, a binder; corn starch, a disintegrant; and stearic acid, a lubricant and glidant; which are filled into a two piece hard gelatin capsule shell. Water is the granulating liquid, and is essentially removed during processing.

Quantitative Composition of Ganciclovir L-Valine Monoester Capsules (One Capsule Three Times Per Day)

Ingredients	Weight Per Capsule (mg)	% W/W
Ganciclovir L-valine monoester hydrochloride	390.00	92.75
Povidone	12.61	3.00
Corn starch	16.81	4.00
Stearic acid[1]	1.05	0.25
Water[2]		
Total fill weight (theoretical)[3]	420.47	100.00

The powder blend is filled into two piece hard gelatin capsule shells.

[1]The amount of stearic acid may vary from 0.1% to 5.0% of the weight.

[2]The amount of water may vary to produce an acceptable granulation, and is dried off.

[3]The total fill weight (theoretical) does not include the residual moisture that will be present in the finished product.

Quantitative Composition of Ganciclovir L-Valine Monoester Capsules (Two Capsules Three Times Per Day)

Ingredients	Weight Per Capsule (mg)	% W/W
Ganciclovir L-valine monoester hydrochloride	312.00	92.75
Povidone	10.09	3.00
Corn Starch	13.45	4.00
Stearic Acid	0.84	0.25
Water[2]		
Total fill weight (theoretical)[3]	336.38	100.00

[1]The amount of stearic acid may vary from 0.1% to 5.0% of the weight.
[2]The amount of water may vary to produce an acceptable granulation, and is dried off.
[3]The total fill weight (theoretical) does not include the residual moisture that will be present in the finished product.

The powder blend is filled into two piece hard gelatin capsule shells.

Example of the Manufacturing Procedure for Ganciclovir L-Valine Monoester Capsules

1. Blend the ganciclovir L-valine monoester and part of the corn starch in a suitable manner.
2. Dissolve the povidone in the water with stirring.
3. Add (2) to (1) while continuing to mix to form a granulation.
4. Mill the wet granulation if necessary.
5. Dry the wet granulation in a dryer.
6. Pass the dry granulation, the remaining corn starch, and the stearic acid through a mill.
7. Blend (6) in a suitable mixer.
8. Encapsulate the appropriate amount of (7) into 2 piece hard gelatin capsule shells.

What is claimed is:

1. The compound 2-(2-amino-1,6-dihydro-6-oxo-purin-9-yl)methoxy-3-hydroxy-1-propanyl-L-valinate hydrochloride in crystalline form.

2. An antiviral pharmaceutical composition comprising the compound of claim 1 and a pharmaceutically acceptable excipient.

3. A method of treating an animal infected with a virus selected from herpes simplex virus and cytomegalovirus, comprising administering a therapeutically effective amount of the compound of claim 1 to the animal.

4. The method of claim 2 where the compound is administered orally.

5. The method of claim 3 where the herpes viral infection is a cytomegalovirus infection.

6. The method of claim 5 wherein the compound is administered orally.

* * * * *

SYNTEX DEVELOPMENT RESEARCH
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HUMAN PHARMACEUTICAL REGULATORY AFFAIRS

May 26, 1995

Central Document Room
Food and Drug Administration
Center for Drug Evaluation and Research
Park Building, Room
5600 Fisher Lane
Rockville, Maryland 20857

RE: Original IND - Notice of Claimed Investigational Exemption for a New Drug, RS-79070-194, Ganciclovir Valinate Hydrochloride.

Dear Reviewers:

On behalf of Syntex Laboratories, Inc., we are submitting a Notice of Claimed Investigational Exemption for RS-79070-194, ganciclovir valinate hydrochloride, a prodrug of ganciclovir (hereafter referred to as RS-79070-194). Enclosed is a signed form FDA-1571 and related material for the IND, pursuant to Section 505(I) of the Food, Drug and Cosmetic Act.

RS-79070-194 will be evaluated in an effort to increase the bioavailability of ganciclovir after oral administration. In animal studies RS-79070-194 has been shown to significantly increase the oral bioavailability of the parent compound ganciclovir.

Ganciclovir is a nucleoside analog of deoxyguanosine having anti-viral activity against the Herpes family of viruses. Ganciclovir has been investigated by Syntex as an intravenous dosage form under IND 25,082 and is the subject of NDA 19-661. Ganciclovir oral capsules have been previously investigated by Syntex under IND 32,149 and are the subject of NDA 20-460. Intravenous ganciclovir was approved in 1989 for the treatment of CMV retinitis in immunocompromised subjects and in 1992 for the prevention of CMV disease in transplant subjects at risk for CMV disease. Oral ganciclovir was approved in 1994 as an alternative to the intravenous formulation for maintenance treatment of CMV retinitis in immunocompromised patients, including patients with AIDS, in whom retinitis is stable following appropriate induction therapy and for whom the risk of more rapid progression is balanced by the benefit associated with avoiding daily IV infusions.

The acute and subchronic (1 month) toxicological profile of RS-79070-194 has been studied in mice and dogs. Reports are submitted in this IND. After oral administration RS-79070 rapidly hydrolizes to ganciclovir and the naturally occuring amino acid valine.

The toxicological profile of orally administered ganciclovir has been extensively evaluated in mice, rats, and dogs. The reports of these studies were submitted to IND 25,082, IND 32,149, NDA 19-661 and NDA 20-460 and are hereby included by reference. This information is believed to be adequate to support clinical dosing in our planned investigational trial.

The first study under this IND will be an open label, randomized, single dose, three way crossover pharmacokinetics study. A total of 18 asymptomatic HIV and CMV seropositive subjects will be entered in order to achieve at least 12 fully evaluable subjects. The objective of this study of to investigate the fasting, single dose pharmacokinetics and absolute and relative bioavailability of RS-79070-194 (in ganciclovir equivalents) as compared to ganciclovir IV and oral. This study will be conducted by Roger Anderson, M.D. FD-1572 and curriculum vitae are contained in Section 6 of this submission. Donald Jung, Ph.D. and Mary Jean Stempien, M.S., M.D. of Syntex Research will monitor the study. Drs. Jung's and Stempien's curricula vitae are contained in Section 6 of this submission.

Copies of the General Correspondence previous to the submission of this IND between Syntex and the Division are included in section 10.

We look forward to working closely with the Division of Anti-Viral Drug Products in the development of this compound. If there are any questions or comments concerning this submission, please contact me at (415) 496-3683 (tel.) or (415) 852-1861 (fax) or Dr. Bonnie Charpentier at (415) 354-2344.

Sincerely,

Hermine Mante

Dr. Hermine Mante
Regulatory Program Manager
Drug Regulatory Affairs

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

INVESTIGATIONAL NEW DRUG APPLICATION (IND)
(TITLE 21, CODE OF FEDERAL REGULATIONS (CFR) Part 312)

Form Approved: OMB No. 0910-0014.
Expiration Date: June 30,1991.
See OMB Statement on Reverse.

NOTE: No drug may be shipped or clinical investigation begun until an IND for that investigation is in effect (21 CFR 312.40).

1. NAME OF SPONSOR
Syntex (U.S.A.) Inc.

2. DATE OF SUBMISSION
May 26, 1995

3. ADDRESS *(Number, Street, City, State and Zip Code)*
3401 Hillview Avenue
Palo Alto, California 94304

4. TELEPHONE NUMBER *(Include Area Code)*
(415) 852-3003

5. NAME(S) OF DRUG *(Include all available names: Trade, Generic, Chemical, Code)*
RS-79070-194, Ganciclovir valinate hydrochloride

6. IND NUMBER *(if previously assigned)*

7. INDICATION(S) *(Covered by this submission)*
Anti-viral (CMV)

8. PHASE(S) OF CLINICAL INVESTIGATION TO BE CONDUCTED: ■ PHASE 1 ☐ PHASE 2 ☐ PHASE 3 ☐ OTHER _____
(Specify)

9. LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS *(21 CFR Part 312)*, NEW DRUG OR ANTIBIOTIC APPLICATIONS *(21 CFR Part 314)*, DRUG MASTER FILES *(21 CFR 314.420)*, AND PRODUCT LICENSE APPLICATIONS *(21 CFR Part 601)* REFERRED TO IN THIS APPLICATION.

Refer to IND 25,082, IND 32,149, NDA 19-661, and NDA 20-460

10. ***IND submissions should be consecutively numbered. The initial IND should be numbered "Serial Number: 000." The next submission (e.g. amendment, report, or correspondence) should be numbered "Serial Number: 001." Subsequent submissions should be numbered consecutively in the order in which they are submitted.***

Serial Number:
000

11. THIS SUBMISSION CONTAINS THE FOLLOWING: *(Check all that apply)*

■ INITIAL INVESTIGATIONAL NEW DRUG APPLICATION (IND) ☐ RESPONSE TO CLINICAL HOLD

PROTOCOL AMENDMENT(S):	INFORMATION AMENDMENT(S):	IND SAFETY REPORT(S):
☐ NEW PROTOCOL	☐ CHEMISTRY/MICROBIOLOGY	☐ INITIAL WRITTEN REPORT
☐ CHANGE IN PROTOCOL	☐ PHARMACOLOGY/TOXICOLOGY	☐ FOLLOW-UP TO A WRITTEN REPORT
☐ NEW INVESTIGATOR	☐ CLINICAL	

☐ RESPONSE TO FDA REQUEST FOR INFORMATION ☐ ANNUAL REPORT ☐ GENERAL CORRESPONDENCE

☐ REQUEST FOR REINSTATEMENT OF IND THAT IS WITHDRAWN, INACTIVATED, TERMINATED OR DISCONTINUED ☐ OTHER _____
(Specify)

CHECK ONLY IF APPLICABLE

JUSTIFICATION STATEMENT MUST BE SUBMITTED WITH APPLICATION FOR ANY CHECKED BELOW. REFER TO THE CITED CFR SECTION FOR FURTHER INFORMATION.

☐ TREATMENT IND 21 CFR 312.35(b) ☐ TREATMENT PROTOCOL 21 CFR 312.35(a) ☐ CHARGE REQUEST/NOTIFICATION 21 CFR 312.7(d)

FOR FDA USE ONLY

CDR/DBIND/DGD RECEIPT STAMP	DDR RECEIPT STAMP	IND NUMBER ASSIGNED:
		DIVISION ASSIGNMENT:

FORM FDA 1571 (12/93) PREVIOUS EDITION IS OBSOLETE

12. **CONTENTS OF APPLICATION**

This application contains the following items: *(check all that apply)*

- ■ 1. Form FDA 1571 *[21 CFR 312.23 (a)(1)]*
- ■ 2. Table of contents *[21 CFR 312.23 (a)(2)]*
- ■ 3. Introductory statement *[21 CFR 312.23 (a)(3)]*
- ■ 4. General investigational plan *[21 CFR 312.23 (a)(3)]*
- ■ 5. Investigator's brochure *[21 CFR 312.23 (a)(5)]*
- 6. Protocol(s) *[21 CFR 312.23 (a)(6)]*
  - ■ a. Study protocol(s) *[21 CFR 312.23 (a)(6)]*
  - ■ b. Investigator data *[21 CFR 312.23 (a)(6)(iii)(b)]* or completed Form(s) FDA 1572
  - ■ c. Facilities data *[21 CFR 312.23 (a)(6)(iii)(b)]* or completed Forms(s) FDA 1572
  - ■ d. Institutional Review Board data *[21 CFR 312.23 (a)(6)(iii)(b)]* or completed Form(s) FDA 1572
- ■ 7. Chemistry, manufacturing, and control data *[21 CFR 312.23 (a)(7)]*
  - ■ Environmental assessment or claim for exclusion *[21 CFR 312.23 (a)(7)(iv)(e)]*
- ■ 8. Pharmacology and toxicology data *[21 CFR 312.23 (a)(8)]*
- ■ 9. Previous human experience *[21 CFR 312.23 (a)(9)]*
- ■ 10. Additional information *[21 CFR 312.23 (a)(10)]*

13. IS ANY PART OF THE CLINICAL STUDY TO BE CONDUCTED BY A CONTRACT RESEARCH ORGANIZATION? ■YES ☐ NO

IF YES, WILL ANY SPONSOR OBLIGATIONS BE TRANSFERRED TO THE CONTRACT RESEARCH ORGANIZATION? ■ YES ☐ NO

IF YES, ATTACH A STATEMENT CONTAINING THE NAME AND ADDRESS OF THE CONTRACT RESEARCH ORGANIZATION, IDENTIFICATION OF THE CLINICAL STUDY, AND A LISTING OF THE OBLIGATIONS TRANSFERRED.

14. NAME AND TITLE OF THE PERSON RESPONSIBLE FOR MONITORING THE CONDUCT AND PROGRESS OF THE CLINICAL INVESTIGATIONS

Donald Jung, Ph.D.
Associate Director
Clinical Research/Clinical Pharmacokinetics

15. NAME(S) AND TITLE(S) OF THE PERSON(S) RESPONSIBLE FOR REVIEW AND EVALUATION OF INFORMATION RELEVANT TO THE SAFETY OF THE DRUG

Mary Jean Stempien, M.D.
Associate Medical Director
Immunology and Infectious Diseases

I agree not to begin clinical investigations until 30 days after FDA's receipt of the IND unless I receive earlier notification by FDA that the studies may begin. I also agree not to begin or continue clinical investigations covered by the IND if those studies are placed on clinical hold. I agree that an Institutional Review Board (IRB) that complies with the requirements set forth in 21 CFR Part 56 will be responsible for the initial and continuing review and approval of each of the studies in the proposed clinical investigation. I agree to conduct the investigation in accordance with all other applicable regulatory requirements.

16. NAME OF SPONSOR OR SPONSOR'S AUTHORIZED REPRESENTATIVE	17. SIGNATURE OF SPONSOR OR SPONSOR'S AUTHORIZED REPRESENTATIVE	
Daniel L. Zabrowski, Ph.D. Executive Director Drug Regulatory Affairs		
18. ADDRESS *(Number, Street, City, State and Zip Code)* 3401 Hillview Avenue Palo Alto, California 94304	19. TELEPHONE NUMBER *(Include Area Code)* (415) 852-3003	20. DATE 05/26/95

(WARNING: A willfully false statement is a criminal offense U.S.C. Title 18, Sec. 1001.)

Roche

Pharmaceuticals

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
12229 Wilkins Avenue
Rockville, Maryland 20859

Palo Alto, September 28, 2000
Re: NDA 21-304 - VALCYT™ (valganciclovir HCl) tablets
Original New Drug Application

Dear Reviewers:

In accordance with 21CFR Part 314.50, Roche Global Development-Palo Alto, a Division of Syntex (U.S.A.) LLC, hereby submits an original New Drug Application for VALCYT™ (valganciclovir HCl) 450 mg tablets, for use in the treatment of cytomegalovirus (CMV) retinitis in subjects with acquired immunodeficiency syndrome (AIDS). The NDA number 21-304 has been pre-assigned to this submission. Valganciclovir has been the subject of IND 48,106. Valganciclovir is a the valyl ester of ganciclovir, which is subject of IND 25,082 ganciclovir sodium, intravenous (RS-21592), NDA 19-661 Cytovene®-IV (ganciclovir sodium for injection), IND 32,149 ganciclovir (RS-21592), NDA 20-460 Cytovene® (ganciclovir capsules).

NDA Copies and Content

This submission consists of an archival copy (182 volumes and 4 CDroms) and the required number of review copies. The archival copy of Items 11 and 12, which contain case report tabulations patient profiles and SAS transport files and documentation, and case report forms are provided only in electronic form. The approximate size of these electronic files is 1.93 Gigabytes (797 MB for Case Report Forms, 47.2 MB for Patient Profiles and 1.09 GB for SAS transport files and documentation). All the electronic files in the submission are provided on CD-ROM and were scanned for viruses with Norton Antivirus, Version 5.01, Symantec Corp. No known viruses were found.

Roche Global Development - Palo Alto a Division of Syntex (U.S.A.) LLC 3401 Hillview Ave.
Palo Alto,
California 94304-1397

Overall NDA Content:	Volume Number
Section 1 - Index and Administrative	1
Section 2 - Labeling	2
Section 3 - Application Summary	3
Section 4 - Chemistry, Manufacturing and Controls	4 - 9
Section 5 - Nonclinical Pharmacology and Toxicology	10 - 35
Section 6 - Human Pharmacokinetics and Bioavailability	36 - 82
Section 7 - Microbiology	83 - 94
Section 8/10 - Clinical and Statistical	95 - 182
Section 11 - Case Report Tabulations	CD-Rom 1- 3
Section 12 - Patient Case Report Forms	CD-Rom 3-4

FDA/Sponsor Key Meetings and Priority Review Request
The development program for valganciclovir has been the subject of various meetings and teleconferences, addressing both clinical and technical aspects of its content. In particular, pre-NDA meetings with the overall review team and CMC review team in December 1999 and June 2000 respectively. From these discussions we understand that this application will receive a priority review.

Finally, several teleconferences with the CMC review team have been held recently to address some late manufacturing issues and their impact on the submission of this NDA.

Based on these discussions this NDA is being submitted with Roche's understanding that the Agency has agreed to accept the NDA with the knowledge that certain required data will be provided during the NDA review, namely:

- Proposed master batch record by November 15, 2000
- 3-month stability data from the registration batches manufactured at Patheon
- 24 month stability data from the stability batches manufactured at Oread

In addition, Roche has agreed to supply release data on all full scale validation batches being manufactured during the review period.

Patent Information
The drug substance in this application is covered by US Patent Number 6,083,953, which issued on July 4, 2000 and expires on July 28, 2014

Pediatric Study Requirements
In accordance with 21CFR. 314.55(c), Roche requests a waiver of the requirements of 314.55 (a) for pediatric patients with CMV retinitis. A rationale for this request was previously submitted as part of a submission to IND 48, 106 on July 25, 2000 (amendment 141) and is attached to this cover letter (Attachment 1).

The archival copy and Reviewer's copies of this NDA are being sent to the Central Document Room for CDER. Desk copies are being sent to the Document Control Room for the Division to the attention of Ms. L. Stephens.

Roche appreciates the continuous support the Division has provided for the development program for VALCYT. We look forward to extending this long-standing collaboration to the review of this application.

Should you have any questions during the course of the review period, please do not hesitate to contact me by phone at (650) 496-3683 or by fax at (650) 852-1861

Sincerely,

H. Mante

Hermine Mante, PharmD.
Senior Regulatory Program Manager

Attachment 1

Rationale for a waiver from the requirements of 21 CFR 314.55(a) for valganciclovir in pediatric patients with CMV retinitis.

In developed countries in the latter part of 1996, highly active antiretroviral therapy (HAART) became widely used in adult and pediatric HIV infected patients. The use of HAART has significantly changed the character of CMV retinitis and has impacted clinical trials of anti-CMV drugs for the treatment of CMV retinitis.

Patients who respond to HAART have significant increases in the CD4 lymphocyte count and decreased HIV viral load. The outcome is a decrease in the number of opportunistic infections and increased patient survival. The number of new cases of CMV retinitis in adults has decreased to 20% or less of the pre-HAART numbers in both the U.S. and Europe [Jacobson et.al.1999, Burman *et al.*, 2000, Frederick *et al.*,2000, Baril *et al*, 1997, Mitchell et al, 1999]. In patients who already have CMV retinitis who respond to HAART, progressions of CMV retinitis are less common, and times to progression are significantly elongated [Chiller, 1998, Mitchell et al, 1999, Davis *et al*, 1999].

A decrease in the incidence of retinitis because of HAART has made enrollment of retinitis trials for adults difficult. For example in the early 1990's a typical trial enrolling adult patients with AIDS and newly diagnosed CMV retinitis took 15 months to enroll 161 patients at 15 locations (0.83 patients/month at each location). Study WV15376, the primary randomized study of valganciclovir, took 28 months to enroll 160 adult patients at 42 locations (0.09 patients/month at each location). Other sponsors conducting studies of CMV retinitis have had similar difficulty. The problem is further exacerbated in studies in the pediatric population where the peri-natal use of antiretrovirals has fortunately decreased the incidence of maternal-fetal transmission in cases where the HIV status is known. As it is not current clinical practice to give prophylactic anti-CMV treatment in asymptomatic disease, attempts to recruit for a pediatric CMV retinitis study would be very difficult.

The Sponsor requests, therefore, that the FDA grant a waiver from the requirements of 21 CFR 314.55(a) for valganciclovir in pediatric patients with CMV retinitis.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: March 31, 2003
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Syntex (U.S.A.) LLC	September 28, 2000
TELEPHONE NO. *(Include Area Code)* 650-496-3683	**FACSIMILE (FAX) Number** *(Include Area Code)* 650-852-1861
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):* 3401 Hillview Avenue Palo Alto, CA 94304	**AUTHORIZED U.S. AGENT NAME & ADDRESS** *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE Hermine Mante, Pharm.D. 3401 Hillview Avenue Palo Alto, CA 94304 Phone: 650-496-3683; Fax: 650-852-1861

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)*

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
valganciclovir hydrochloride	VALCYT ™

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*	CODE NAME *(If any)*
L-Valine, ester with 9-[[2-hydroxy-1-(hydroxymethyl)-ethoxy]methyl]guanine, monohydrochloride	Ro 107-9070/194

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Tablets	450 mg (free base)	Oral

(PROPOSED) INDICATION(S) FOR USE:
Treatment of cytomegalovirus (CMV) retinitis in patients with acquired immunodeficiency syndrome (AIDS)

APPLICATION INFORMATION

APPLICATION TYPE *(check one)* ☑ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94) ☐ BIOLOGICS LICENSE APPLICATION (21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☐ 505 (b)(1) ☐ 505 (b)(2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug — Holder of Approved Application

TYPE OF SUBMISSION *(check one)* ☑ ORIGINAL APPLICATION ☐ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION ☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION New Drug Application

PROPOSED MARKETING STATUS *(check one)* ☑ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 182 — THIS APPLICATION IS ☐ PAPER ☑ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Please see attached Form 356H Establishment Information

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

IND 48,106; IND 25,082; IND 32,149; NDA 19-661; NDA 20-460; see attached Form 356H Cross-References for list of DMFs

This application contains the following items: *(Check all that apply)*	
✘	1. Index
✘	2. Labeling *(check one)* ☑ Draft Labeling ☐ Final Printed Labeling
✘	3. Summary (21 CFR 314.50 (c))
✘	4. Chemistry section
✘	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
✘	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
✘	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
✘	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
✘	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
✘	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
✘	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
✘	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
✘	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
✘	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
✘	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
	15. Establishment description (21 CFR Part 600, if applicable)
✘	16. Debarment certification (FD&C Act 306 (k)(1))
✘	17. Field copy certification (21 CFR 314.50 (k)(3))
✘	18. User Fee Cover Sheet (Form FDA 3397)
✘	19. Financial Information (21 CFR Part 54)
	20. OTHER *(Specify)*

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
H. Mante	Hermine Mante, Pharm.D. Senior Regulatory Program Manager	September 28, 2000

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
3401 Hillview Avenue, Palo Alto, CA 94304	(650) 496-3683

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CDER, HFD-94
12420 Parklawn Dr., Room 3046
Rockville, MD 20852

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

FORM FDA 356h (4/00)

CORRESPONDENCE LOG – TESTING PHASE

SUBMISSION TYPE AND NO.: IND 48,106

PRODUCT TITLE Ganciclovir Valinate Hydrochloride

DT SENT	DT REC'D	SERIAL#	SYNOPSIS
May 26 95			ORIGINAL SUBMISSION - notice of claimed investigational exemption for a new drug, RS 79070-194, Ganciclovir Valinate Hydrochloride.
Jun 05 95	Jun 08 95		ACKNOWLEDGMENT of receipt of original submission and assignment of IND #.
Jun 26 95		001	AMENDMENT - Information Amendment: Clinical: copy of case report forms for study.
Aug 14 95	Aug 17 95		LETTER to Applicant from FDA, re: Teleconference on June 29, 1995; proposed study may proceed; request for information.
Nov 09 95		002	AMENDMENT-Information Amendment: Chemistry/Microbiology: re: Final printed labels for Study.
Feb 19 96		002(003)	Background Information to request meeting for discussion of clinical plan
Feb 29 96		004	Re: Correction of Amendment #002 on Feb 19 to #003
Apr 03 96		005	Revised Background information for meeting
Apr 04 96		006	**AMENDMENT** - Information Amendment: Clinical: Pharmacokinetic & Bioavailability study in HIV and CMV seropositive subjects
Apr 26 96		007	Revised Background information for meeting on May 9 re: Phase I Clinical Study
Jun 11 96			LETTER: From FDA to Applicant re: list of issues for clinical study.
7Jun 20 96		008	**AMENDMENT** - Protocol Amendment:New Protocol
Jun 20 96		009	First Annual Progress Report -(Includes CMC changes)

CORRESPONDENCE LOG – TESTING PHASE

SUBMISSION TYPE AND NO.: IND 48,106

PRODUCT TITLE Ganciclovir Valinate Hydrochloride

DT SENT	DT REC'D	SERIAL#	SYNOPSIS
Jul 09 96		010	**AMENDMENT** - Protocol Amendment: New Investigators
Aug 08 96		011	**AMENDMENT** - Protocol Amendment: Change in Protocol for **WP15347**; ProtocolAmendment: New Investigator for **WP15347**
10	Aug 22 96	012	**AMENDMENT** Protocol Amendment: Change in Protocol: for **WP15347**; Protocol Amendment : New Investigator
Aug 26 96		013	**CORRESPONDENCE**: Gantt chart for toxicology studies
Oct 07 96		014	**SUBMISSION**: Draft Protocol for WV15376 and Revised Development Program
Dec 09 96		015	**AMENDMENT** - Protocol Amendment: New Protocol for Study **WV15376B,**
Dec 18 96		016	**SUBMISSION** - Request for Meeting with FDA to discuss program
Jan 09 97			**FAX** - From FDA to Applicant - comments on amendment #014 and requesting response.
Jan 13 97		017	**FAX** - Response to questions from Dr. Davit.
Jan 13 97		017	**RESPONSE** - Response to questions from Dr. Davit
Jan 14 97		018	**AMENDMENT** - Information Amendment: Chemistry/Microbiology
Jan 15 97		019	**SUBMISSION** - Background package for meeting with FDA to discuss clinical plan
Jan 24 97		020	**FAX** - Response to questions from Dr. Davit.
Jan 24 97		020	**AMENDMENT** - Response to questions from Dr. Davit

CORRESPONDENCE LOG – TESTING PHASE

SUBMISSION TYPE AND NO.: IND 48,106

PRODUCT TITLE Ganciclovir Valinate Hydrochloride

DT SENT	DT REC'D	SERIAL#	SYNOPSIS
Jan 27 97		021	**AMENDMENT** - Errata for the background package for the February 3, 1996 meeting
Jan 27 97			**FAX** - from Dr. Davit
Jan 30 97		022	**AMENDMENT** - Response to questions from Dr. Davit
Feb 14		023 (022)	**AMENDMENT** - Protocol Amendment: New Investigators
Feb 18 97		024	**AMENDMENT** - Correction to amendment numbers.
Mar 04 97		025	**AMENDMENT** - Protocol Amendment: New Protocol
Mar 04 97		026	**AMENDMENT** - Draft Protocol
Mar 19 97		027	**AMENDMENT** - Protocol Amendment: New Investigators for Study No. **WV15376**
Mar 25 97		028	**AMENDMENT** - Draft Protocol
Apr 4 97			**FAX** - From Terrie Crescenzi (on behalf of Dr. J. Martin)
Apr 14 97		029	**AMENDMENT** - Protocol Amendment: New Investigators; Information Amendment: Clinical - Addition of Clinical Laboratory site
Apr 16 97			**FAX** - From FDA, comments and request for reponse re amendment #026
Apr 17 97			**FAX** - To Tony Zeccola with names of Roche participants in Apr 16 teleconference and publication reprint.
Apr 22 97	Apr 23 97		**FAX** - From FDA, comments and request re amendment #028.

CORRESPONDENCE LOG – TESTING PHASE

SUBMISSION TYPE AND NO.: IND 48,106

PRODUCT TITLE Ganciclovir Valinate Hydrochloride

DT SENT	DT REC'D	SERIAL#	SYNOPSIS
Apr 24 97		030	**GENERAL CORRESPONDENCE –** Communication re decision to place hold on development of ganciclovir prodrug.
Apr 24 97			**FAX** - Communication reqarding decision to place on hold the development of ganciclovir prodrug.
Apr 28 97			**FAX** - To FDA with names of Roche particpants in Apr 25 97 teleconference. Second transmission of fax sent Apr 25 97.
Apr 28 97			**FAX** - To FDA with draft minutes of telecon on Apr 25 97.
May 07 97		031	**GENERAL CORRESPONDENCE** – Minutes of April 15 telecon with FDA Division of Antiviral Drug Products
May 15 97	May xx 97		**LETTER** – from FDA requesting alternative plans for development of ganciclovir prodrug.
Jun 04 97		032	**AMENDMENT** – Change in Protocol.
Jul 18 97		033	**SECOND ANNUAL REPORT - Mar 26 96 through Mar 25 96**
Aug 8 97		034	**OTHER**: Background package for FDA meeting on Sep 10
Sep 5 97		035	**GENERAL CORRESPONDENCE**
Sep 5 97	Sep 5 97		**FAX** - To FDA
Sep 9 97		036	**GENERAL CORRESPONDENCE –**
Sep 9 97	Sep 9 97		**FAX** - To FDA
Sep 17 97		037	**AMENDMENT** - Protocol - New InvestigatorS
Sep 18 97	Sep 18 97		**FAX** - Draft minutes of Sep 10 97 meeting.
Sep 25 97	Sep 25 97		**FAX** - To FDA with draft minutes of Sep 10 97 meeting.

CORRESPONDENCE LOG – TESTING PHASE

SUBMISSION TYPE AND NO.: IND 48,106

PRODUCT TITLE Ganciclovir Valinate Hydrochloride

DT SENT	DT REC'D	SERIAL#	SYNOPSIS
Oct 21 97	Oct xx 97		**LETTER -** from A. DeCicco. with minutes of Sep 10 97.
Nov 17 97		038	**AMENDMENT** - Protocol Amendment: New Investigators Labels in Spanish for Dr. Sierra-Madero's site attached
Dec 09 97		039	AMENDMENT - Request for a telecon to discuss the draft amendment **WV15376D**, a draft protocol for an open pharmacokinetics study in liver transplant recipients **WP15711**. Submission includes an outline of the overall clinical development plan.
Dec 19 97		040	**AMENDMENT**: Protocol: New Investigators
		(040)	**Amendment**: Information: Clinical Protocol; Investigators; change in site name.
Jan 07 98	Jan 07 98		**FAX** from FDA re comments on amendment #039
Jan 12 98	Jan 13 98		**FAX** from FDA re comments on #039.
Jan 14 98		041	**AMENDMENT** - Protocol - Change in Protocol
Jan 29 98		042	**AMENDMENT** - Protocol - New Investigators; Deletion of Subinvestigator:
Feb 6 98		043	**AMENDMENT**: Protocol - New Protocol for study WV15711
Feb 18 98		044	**AMENDMENT**: Protocol - New Protocol for study WV15705

CORRESPONDENCE LOG – TESTING PHASE

SUBMISSION TYPE AND NO.: IND 48,106

PRODUCT TITLE Ganciclovir Valinate Hydrochloride

DT SENT	DT REC'D	SERIAL#	SYNOPSIS
Feb 20 98		045	**OTHER** - Letter and CVs of members of the expert review board
Feb 26 98		046	**AMENDMENT** - Protocol: New Investigators
Mar 16 98		047	**AMENDMENT** - Protocol: New protocol WV15511
Apr 13 98		048	**AMENDMENT** - Protocol – New Investigator
			AMENDMENT - Information- Clinical
May 15 98		049	**AMENDMENT** - Protocol - Amendment: Information: Chemistry/Microbiology
Jun 08 98		050	**AMENDMENT** - Protocol: Change in Protocol New Investigator
Jul 7 98		051	**AMENDMENT** – Protocol: New Investigator
		(051)	**AMENDMENT**: Information: Clinical
Jul 7 98		052	**OTHER** – Draft protocol for study
Jul 8 98		053	**AMENDMENT** – Protocol – New Investigator Subinvestigators **New Investigator**
Jul 16 98		054	**AMENDMENT** – Protocol – New Investigator
Jul 17 98		055	**ANNUAL REPORT** Third Annual Report Mar 26 97 to Mar 25 98
Jul 29 98		056	**AMENDMENT** – Protocol: Change in Protocol
Aug 6 98		057	**AMENDMENT** – Protocol: New Investigators; Information: Chemistry/Microbiology Study labels for study sites

CORRESPONDENCE LOG – TESTING PHASE

SUBMISSION TYPE AND NO.: IND 48,106

PRODUCT TITLE Ganciclovir Valinate Hydrochloride

DT SENT	DT REC'D	SERIAL#	SYNOPSIS
Aug 14 98		058	**AMENDMENT** – Protocol: New Protocol Clinical Trial Formulation for 450 mg tablets: Information: Chemistry/Microbiology for studies
Sep 3 98		059	**GENERAL CORRESPONDENCE** – SAE report
Sep 8 98		060	**AMENDMENT** – Protocol: New Investigator Information: Chemistry /Microbiology – labels for Study WV15509; Information : Clinical – for Study WV 15376
Sep 14 98		061	**GENERAL CORRESPONDENCE – SAE report**
Sep 18 98		062	**AMENDMENT** – Protocol Amendment: New Investigator; Information Amendment: Clinical
Sep 24 98			**FAX** – to FDA –SAE report
Sep 25 98		063	**SAE** – Study WV 15376
Sep 29 98		064	**AMENDMENT** – Protocol Amendment; Study WV15376 new investigators; labels for Canada and U.S.; study 15705 new investigators; labels for sites.
Sep 29 98		065	**GENERAL CORRESPONDENCE** – Regarding current status of trials:
Oct 2 98		066	**SAE** –Study WV15376
Oct 28 98		067	**AMENDMENT** – Information: Clinical – Protocol study WV15511

CORRESPONDENCE LOG – TESTING PHASE

SUBMISSION TYPE AND NO.: IND 48,106

PRODUCT TITLE Ganciclovir Valinate Hydrochloride

DT SENT	DT REC'D	SERIAL#	SYNOPSIS
	Oct 29 98		**FAX** – from FDA dated Oct 23 98. Comments on behalf of Dr. Vanitha Sekar directed to /#058.
Nov 2 98			**FAX** – to FDA - confirmation of meeting requested for Dec 16 98 with list of preliminary questions.
Nov 2 98		068	**OTHER** – Confirmation of meeting requested for Dec 16 98 with list of preliminary questions.
Nov 6 98		069	**RESPONSE** to FDA Request for Information received by fax on Oct 29 98 regarding fed vs. fasting conditions used in protocol for study.
Nov 20 98		070	**OTHER** – Submission of Background Package
Nov 30 98		071	**AMENDMENT** – Information: Clinical
Dec 8 98		072	**OTHER** – addendum to briefing package containing summary table for the mean pharmacokinetic parameters.
Dec 11 98			**FAX** – to FDA with copies of slides for presentation on Dec 16 98.
Dec 11 98		073	**OTHER** - Copies of slides for presentation on Dec 16 98.
28	Dec 23 98	074	**AMENDMENT** – Information: Clinical: subinvestigator and site information
Jan 11 99			**FAX** – to FDA, CSO, with draft minutes Dec 16 98 meeting between Roche and FDA re development program for valganciclovir in transplantation.
Jan 11 99		075	**OTHER** – Draft minutes of Dec 16 98 meeting between Roche and FDA re development program for valganciclovir in transplantation.
Jan 14 99	Jan 25 99		**LETTER** – FDA minutes of Dec 16 98 meeting to

CORRESPONDENCE LOG – TESTING PHASE

SUBMISSION TYPE AND NO.: IND 48,106

PRODUCT TITLE Ganciclovir Valinate Hydrochloride

DT SENT	DT REC'D	SERIAL#	SYNOPSIS
			discuss clinical development of valganciclovir and prevention of CMV disease in solid organ transplant recipients.
Jan 26 99		076	**AMENDMENT** – Protocol: New Investigator; Information: Clinical for Study
Feb 5 99		077	**AMENDMENT**: Information: Chemistry/ Microbiology – Submission of an updated stability statement for the Valganciclovir 450 mg tablets
Feb 16 99		078	**GENERAL CORRESPONDENCE** – Submitting trademarks for review by the FDA Nomenclature Committee
Feb 22 99		079	**OTHER** -Request for a teleconference to discuss scope of the NDA submission for retinitis
Feb 26 99		080	**AMENDMENT** - Information - Clinical: investigator and site information
Feb 26 99			**FAX** to FDA re **SAE**: Study WV15705, Feb 9 99.
Feb 26 99		081	**SAE** - MCN #109129, Study WV15705, patient #3554
Dated Mar 11 99 sent Mar 16 99	Mar 17 99		**FAX** – from FDA : comments on behalf of Dr. K. Reynolds directed towards serial #079
Mar 11 99		082	**OTHER**: Letter confirming telecon for 9 a.m. EST, Mar 16 99
Mar 11 99			**FAX** - from H.Mante to FDA, letter confirming telecon for 9 a.m. EST, Mar 16 99
Mar 24 99			**FAX** - to FDA with **SAE** study WV15376
Mar 24 99		083	**SAE** - study WV15376, Mar 17 99.

CORRESPONDENCE LOG – TESTING PHASE

SUBMISSION TYPE AND NO.: IND 48,106

PRODUCT TITLE Ganciclovir Valinate Hydrochloride

DT SENT	DT REC'D	SERIAL#	SYNOPSIS
Mar 29 99		084	**AMENDMENT** - Information –Clinical: investigator information.
Mar 31 99		085	**SAE** study WV15376
			SAE - study W15705
Apr 15 99		086	**SAE** - study WV15376
Apr 16 99		087	**OTHER** - Request for an early May 99 telecon;
Apr 23 99		088	**SAE** - study 15705
Apr 26 99		089	**RESPONSE to REQUEST** re FDA comments faxed on Mar 11 99
Apr 27 99		090	**AMENDMENT**- Information Amendment - Pharmacology/ Toxicology with reports
May 3 99		091	**SAE** - Study WV15705
May 25 99		092	**AMENDMENT** – Update title and Information
Jun 21 99		093	**GENERAL CORRES** - Correction page for briefing document submitted to #087 Apr 16 99.
Jul 1 99			**FAX** – to C. Kelly with submission of #094.
Jul 1 99		094	**GENERAL CORRES** - Discussion questions for Jul 7 99 telecon and list of proposed Roche participants.
Jul 8 99		095	**SAE** –study WV15376
Jul 19 99		097	**SAE** –Study WV15376
Jul 21 99	Jul 21 99		**FAX** – from FDA with biopharmaceutical comment on /#089.
Jul 21 99		098	**GENERAL CORRES** – Submission of proposed trademarks to FDA Nomenclature Committee.
Aug 16 99			**FAX** – to C. Kelly with #099 submission.

CORRESPONDENCE LOG – TESTING PHASE

SUBMISSION TYPE AND NO.: IND 48,106

PRODUCT TITLE Ganciclovir Valinate Hydrochloride

DT SENT	DT REC'D	SERIAL#	SYNOPSIS
Aug 16 99		099	**GENERAL CORRES** – List of experts in CMV, particularly transplantation, for closed session of Antiviral Advisory Committee.
Aug 19 99		100	**ANNUAL REPORT – Mar 26 98 to Mar 25 99**
Aug 25 99		101	**GENERAL CORRES** - Journal articles, book chapters and original research articles relevant to endpoints of transplantation protocol PV16000.
Sep 8 99			**FAX** - to FDA with submission of #102
Sep 9 99		102	**OTHER** - *Draft* Advisory Committee briefing package.
Sept 10 99	Sep 10 99		**FAX** - from R. Stover listing material needed by the FDA to organize the Oct 4&5 99 Antiviral Drugs Advisory Committee meeting.
Sep 13 99			**FAX** - to FDA with copy of Sep 10 99 fax from L. Stover.
Sep 16 99		104	**AMENDMENT** - Protocol - New Investigator: **Amendment** - Information- Clinical
Sep 17 99	Sep 17 99		**FAX** - from FDA with revised list of material needed for Oct 4-5 99 Antiviral Drugs Advisory Committee.
45	Sep 17 99	105	**OTHER** - Submission of requested items to Antiviral Drugs Advisory Committee for closed session meeting on Oct 5 99.
Sep 27 99		106	**AMENDMENT** - Protocol - New Protocol for Study **PV16000**
Sep 28 99		107	**OTHER** - Response to item 3 requested in preparation for Antiviral Drugs Advisory Committee meeting.
Sep 29 99			**FAX** - to FDA with name of Roche presenter

CORRESPONDENCE LOG – TESTING PHASE

SUBMISSION TYPE AND NO.: IND 48,106

PRODUCT TITLE Ganciclovir Valinate Hydrochloride

DT SENT	DT REC'D	SERIAL#	SYNOPSIS
Oct 1 99			**FAX** - from H.Mante to FDA with #108.
Oct 4 99			**GENERAL CORRES** - Copy of slides that will be used at closed session of Advisory Committee meeting on Oct 5 99.
Oct 8 99		109	**AMENDMENT** - Information - Pharmacology/ Toxicology: Research
Oct 21 99		110	**GENERAL CORRES** - Two issues proposed for discussion at Oct 19 99 telecon
Oct 21 99	Oct 21 99	111	**GENERAL CORRES** - Requesting a pre-NDA meeting in late November/early December .
Oct 22 99		112	**SAE** - Study WV 15376
Oct 27 99	unknown		**FAX** - from FDA with clinical and statistical comments directed toward #106, **PV16000**.
Oct 28 99 (sent Oct 29 99)			**FAX** - to FDA with "Definition of CMV Syndrome for Primary Analysis."
Oct 29 99			**FAX** - to FDA with names of Roche participants in Oct 29 99 telecon.
Nov 3 99			**FAX** - to FDA with second transmission of Oct 29 99 fax
Nov 4 99	Unknown		**FAX** - from FDA with SAS code for obtaining adjusted confidence intervals as discussed in Oct 29 99
Nov 4 99		113	**OTHER** - Submission of background package for pre-NDA meeting on Dec 1 99.
Nov 8 99		114	**SAE** - Study WV15376
Nov 12 99	Unknown		**FAX** - from FDA with reviewers' clinical pharmacology comments on #106
Nov 19 99			**FAX** - to FDA with summary of a 7-day alert report

CORRESPONDENCE LOG – TESTING PHASE

SUBMISSION TYPE AND NO.: IND 48,106

PRODUCT TITLE Ganciclovir Valinate Hydrochloride

DT SENT	DT REC'D	SERIAL#	SYNOPSIS
			for open label safety study
Nov 19 99		115	**SAE** - Summary of 7-day alert report, study WV 15705
Nov 23 99		116	**AMENDMENT** - Protocol - New Investigator: Information – Clinical; reports W-144111 and W-144128 and abstract of results WV15376 Information - Pharmacology/Toxicology:
Nov 24 99		117	**SAE** – study WV15705
Nov 24 99		118	**RESPONSE TO FDA REQUEST** re comments on new protocol: #106 (PV16000)
Dec 13 99		119	**RESPONSE TO FDA REQUEST** re comments on new protocol: #106 (PV16000)
Dec 13 99		120	**AMENDMENT**: Protocol: Change in Protocol – PV16000
Dec 15 99		121	**OTHER:** Submission of Roche draft minutes of Dec 1 99 meeting with copy of slides used at meeting.
Dec 20 99			**FAX**: to FDA, current list of investigators who recruited patients in studies
Dec 21 99		122	**RESPONSE TO FDA REQUEST** : Current list of investigators who recruited patients in studies
Dec 21 99		123	**AMENDMENT**: Protocol: New Investigator Information:Clinical:
56-57	Dec 23 99	124	**AMENDMENT**: Information: Chemistry/Microbiology Manufacturing and packaging site for PV16000 clinical trial supplies CMC Information for Placebo to match Ro 107-9070 film-coated tablets Information : ClinicalBlank case report forms for study **PV16000**

CORRESPONDENCE LOG – TESTING PHASE

SUBMISSION TYPE AND NO.: IND 48,106

PRODUCT TITLE Ganciclovir Valinate Hydrochloride

DT SENT	DT REC'D	SERIAL#	SYNOPSIS
Dec 23 99		125	**SAE**: study WV15705
Jan 21 00		126	**AMENDMENT**: Protocol: New Investigator Information: Chemistry/Microbiology Revised summary report on the comparison of the dissolution profiles of the proposed commercial and clinical trial formulations for valganciclovir tablets.
Mar 1 00	Mar 8 00		**LETTER** - with copy of FDA minutes of Dec 1 99 pre-NDA meeting. Original signatures of minutes preparer and conference chair are on document.
Mar 10 00		127	**SAE** – Mfr #97048, study **WV15376**, patient #2202, Dr. J. Sierra-Madero, 2nd F, Mar 28 98.
Mar 22 00		128	**AMENDMENT** - Protocol – New Investigator/site information.
Apr 19 00		129	**AMENDMENT** – Protocol – Change in Protocol Protocol Amendment: New Investigator **Add** co-investigator: Information Amendment:Chemistry/Microbiology: Informaiton Amendment: clinical Add clinical laboratory
Apr 20 00			**FAX** - to M. Truffa, CDER, with cross reference letter in support of IND 60,075, study ACTG 5030.
Apr 20 00		130	**OTHER** - Investigator IND cross reference letter in support of IND 60,075, protocol ACTG 5030
May 5 00		131	**OTHER** - Meeting request and background information for CMC preNDA meeting on Jun 5 00
May 19 00		132	**AMENDMENT** - Protocol - New Investigator information Information Amendment: Clinical:
May 23 00			**FAX** - to FDA, CDER, with reponse to request for information

CORRESPONDENCE LOG – TESTING PHASE

SUBMISSION TYPE AND NO.: IND 48,106

PRODUCT TITLE Ganciclovir Valinate Hydrochloride

DT SENT	DT REC'D	SERIAL#	SYNOPSIS
May 23 00		133	**RESPONSE TO FDA REQUEST** - Table of chemical structures of the organic impurities for valganciclovir.
May 26 00			**FAX** - to FDA, CDER, with list of questions for the CMC pre-NDA meeting scheduled for Jun 5 00 and the planned Roche attendees.
Jun 16 00		134	**OTHER** - Proposal for electronic submissions of Sections 10, 11 and 12 of valganciclovir NDA.
Jun 16 00		135	**AMENDMENT** - Protocol - New Investigator Information Amendment: Clinical: **OTHER** – Change in the legal entity of the sponsor to: Syntex (U.S.A.) **LLC**
Jun 23 00		136	**ANNUAL REPORT** Mar 26 99 to Mar 25 00
Jul 10 00		137	**OTHER** - Submission of two trademarks for review: **VALCYT** and **CYGANCE.**
Jul 19 00			**FAX** - to FDA with 7-day alert report for open label safety study WV15705.
Jul 19 00		138	**OTHER** - Summary of 7-day alert report for open label safety study WV15705.
Jul 20 00		139	**AMENDMENT** - Protocol - New Investigator Information Amendment: Pharmacology/ Toxicology with final study reports: Information Amendment: Clinical **Add** clinical lab
Jul 24 00			**FAX** - to FDA with list of Roche participants for Jul 24 00 E-sub telecon.
Jul 24 00		140	**SAE** - Study WV15705
Jul 25 00		141	**OTHER** - Proposed pediatric study request and request for partial waivers from pediatric testing

CORRESPONDENCE LOG – TESTING PHASE

SUBMISSION TYPE AND NO.: IND 48,106

PRODUCT TITLE Ganciclovir Valinate Hydrochloride

DT SENT	DT REC'D	SERIAL#	SYNOPSIS
			requirements.
Aug 2 00		142	**OTHER** - Proposed format for additional "simplified" efficacy dataset for study WV15376 as requested during Jul 24 00 telecon.
Aug 9 00	Aug 9 00		**FAX** - from FDA with comments on submission of Jun 16 00 (#134).
Aug 15 00	Aug 21 00		**LETTER** with copy of FDA minutes of pre-NDA CMC meeting of Jun 5 00.
Aug 16 00	Aug 16 00		**FAX** - from CDER re User Fees.
Aug 18 00		143	**AMENDMENT** - Protocol Amendment - New Investigator information; Information Amendment: Clinical
Aug 22 00			**FAX** - to CDER, with copy of #144.
Aug 22 00		144	**OTHER** - Request for concurrence of proposal regarding submittal of NDA without the proposed commercial master batch record and to provide this information during review.
Aug 28 00		145	**SAE** - Study WV15705
Sep 6 00	Sep 6 00		**FAX** – from FDA with comments to CMC amendment dated Aug 22 00.
Sep 21 00		146	**AMENDMENT** – Protocol Amendment – New Investigator information
Sep 25 00			**FAX** – to FDA with proposal for submission of retinal images for pivotal study
Sep 25 00		147	**OTHER** – In response to fax of Aug 9 00 re #134, retinal imaging from pivotal efficacy study

CORRESPONDENCE LOG – APPLICATION PHASE

SUBMISSION TYPE AND NO.: NDA 21-304

PRODUCT NAME: Valcyte™ (valganciclovir HCl) 450 mg Tablets

DATE SENT	DATE RCVD	SUPP#	SYNOPSIS
Sep 28 00			**ORIGINAL SUBMISSION** for Valcyt (valganciclovir HCl) 450 mg tablets for treatment of cytomegalovirus (CMV) retinitis in patients with AIDS.
Oct 9 00			**OTHER**– response to Oct 9 00 FDA phone request for list of investigators and copy of protocol for primary efficacy study.
Oct 11 00			**SUBMISSION** – Reviewers aid containing the original retinal images related to pivotal efficacy study.
Oct 13 00			**SUBMISSION** in response to phone request on Oct 11 00 for information on three investigators.
Oct 31 00	Nov 6 00		**ACKNOWLEDGMENT** of receipt of application for Valcyt dated Sep 28 00 and received Sep 29 00.
Nov 9 00			**LETTER** – stating that the Sponsor of 21-304 has no objections between interactions between FDA and Therapeutic Products Programme of Canada.
Nov 10 00			**SUBMISSION** – containing desk copy of files in CD-ROM format.
Nov 16 00			**SUBMISSION** – with proposed commercial Master Batch Record (MBR), found in Attachment 1. Dissolution information is provided in Attachment 2.
Nov 16 00			**LETTER** to FDA San Francisco Field Office with copy of Nov 16 00 submission.
Nov 27 00			**FAX** - from Applicant to FDA with response to questions (see response below).
Nov 27 00			**RESPONSE** to questions raised at Nov 2 00 telecon re possible impact of HAART during

CORRESPONDENCE LOG – APPLICATION PHASE

SUBMISSION TYPE AND NO.: NDA 21-304

PRODUCT NAME: Valcyte™ (valganciclovir HCl) 450 mg Tablets

DATE SENT	DATE RCVD	SUPP#	SYNOPSIS
			randomized portion of study WV15376.
Dec 1 00			**SUBMISSION** - of additional datasets containing HIV RNA and CD4 results.
Dec 12 00			**SUBMISSION** – Resubmission of additional datasets submitted on Dec 1 00. Corrected data supplied on diskette.
Dec 14 00	Dec 14 00		**FAX** – from T. Turner (CDER) to Applicant with request for agenda information for Feb 27 01 meeting of Antiviral Drugs Advisory Committee.
Jan 3 01			**FAX** – from Applicant to FDA with questions related to Advisory Committee briefing package.
Jan 9 01	Jan 9 01		**FAX** – from FDA to Applicant with tradename review for Valcyt (valganciclovir).
Jan 9 01			**EMAIL** – Draft copy of Advisory Committee Briefing Package.
Jan 9 01			**FAX** – Draft copy of Advisory Committee Briefing Package.
Jan 9 01			**SUBMISSION** – Draft copy of Advisory Committee Briefing Package.
Jan 10 01	Jan 10 01		**FAX** – from FDA to Applicant with biopharmaceutical comments on GANS2226 and request for explanation.
Jan 10 01			**EMAIL** – from Applicant to FDA with copy of the draft briefing document dated Jan 9 01
Jan 15 01			**EMAIL** – from Applicant to FDA with requested ID numbers for withdrawals.
Jan 15 01			**EMAIL** – from Applicant to FDA with explanation of corporate relationships of Syntex (U.S.A.) LLC as they affect valganciclovir.

CORRESPONDENCE LOG – APPLICATION PHASE

SUBMISSION TYPE AND NO.: NDA 21-304

PRODUCT NAME: Valcyte™ (valganciclovir HCl) 450 mg Tablets

DATE SENT	DATE RCVD	SUPP#	SYNOPSIS
Jan 15 01			**EMAIL** – from Applicant to FDA with ID numbers for withdrawals for WV 15376.
Jan 15 01			**EMAIL** – from Applicant to FDA with explanation of Roche Holdings, Inc. corporate relationships.
Jan 16 01			**SUBMISSION** – 4-Month Safety Update and Item 12, updated case report forms.
Jan 16 01			**EMAIL** – from FDA to Applicant re receipt of email of ID numbers sent Jan 15 01.
Jan 16 01			**SUBMISSION** – As requested on Jan 12 01, electronic copy of vols. 80 and 81 of NDA 21-304.
Jan 18 01	Jan 18 01		**FAX** – from FDA to Applicant with comments on the draft Advisory Committee background package.
Jan 19 01			**FAX** – to FDA from Applicant with response to questions sent on Jan 10 01.
Jan 19 01			**SUBMISSION** – Response to questions (dosing history and others) raised on Jan 10 01.
Jan 22 01	Jan 22 01		**FAX** – from FDA to Applicant with pharmacometric comments re study GANS2226.
Jan 22 01			**EMAIL** – from FDA to Applicant with attendees for Jan 24 01 telecon; pharmacometric comments re study GANS2226
Jan 22 01			**EMAIL** – from Applicant to FDA with Word file containing ID numbers for progressors and non-evaluable patients at week 4.
Jan 23 01			**SUBMISSION** – Diskette containing proposed package insert for Valcyt™.
Jan 23 01			**EMAIL** - from FDA to Applicant with fax of

CORRESPONDENCE LOG – APPLICATION PHASE

SUBMISSION TYPE AND NO.: NDA 21-304

PRODUCT NAME: Valcyte™ (valganciclovir HCl) 450 mg Tablets

DATE SENT	DATE RCVD	SUPP#	SYNOPSIS
			ophthalmalogic comments.
Jan 23 01	Jan 23 01		**FAX** – from FDA to Applicant with ophthalmalogic comments.
Jan 23 01			**EMAIL** – from Applicant to FDA with names of Roche staff and consultants for Jan 24 01 telecon.
Jan 23 01			**SUBMISSION** – Briefing document(s) dated Jan 22 01 for Feb 27 01 meeting of the Antiviral Drugs Advisory Committee.
Jan 26 01	Jan 26 01		**FAX** – from FDA to Applicant with comments re AC background package.
Jan 26 01	Jan 26 01		**FAX** – from FDA to Applicant with notice of public advisory meeting and agenda for Antiviral Drugs Advisory Committee on Feb 27 01.
Jan 26 01			**SUBMISSION** – "FDA Advisory Committee Briefing Document for Valganciclovir HCl in the Treatment of CMV Retinitis in AIDS Patients, NDA 21-304, 22 January 2001"
Jan 26 01			**SUBMISSION** – As requested, two CDs each containing the briefing document for the Feb 27 01 meeting of the Antiviral Drugs
Jan 30 01			**FAX** – to FDA from Applicant with cover letter of submission re valganciclovir presentation at Feb 14-16 01 NIH-NIAID meeting.
Jan 30 01			**SUBMISSION** – Draft of agenda for NIH-NIAID Collaborative Antiviral meeting Feb 14-16 01 at which Roche physician will be making presentation.
Jan 30 01			**FAX** – from Applicant to FDA with response to questions sent on Jan 23 01.

CORRESPONDENCE LOG – APPLICATION PHASE

SUBMISSION TYPE AND NO.: NDA 21-304

PRODUCT NAME: Valcyte™ (valganciclovir HCl) 450 mg Tablets

DATE SENT	DATE RCVD	SUPP#	SYNOPSIS
Jan 30 01			**SUBMISSION** - Response to questions sent on Jan 23 01.
Jan 31 01			**FAX** – from Applicant to FDA with response to questions sent on Jan 22 01.
Jan 31 01			**SUBMISSION** – Response to questions sent on Jan 22 01
Jan 31 01			**EMAIL** – from Applicant to FDA with request for clarification on comment dated Jan 26 0l.
Feb 02 01			**EMAIL** – from Applicant to FDA with ID numbers, as requested, for patients with Zone 1 CMVR at baseline.
Feb 05 01			**LETTER** with list of advisors attending Antiviral Drugs Advisory Committee on Feb 27 01
Feb 6 01	Feb 06 01		**FAX** – from FDA to Applicant with ophthalmologic consult comments.
Feb 7 01			**FAX** – from Applicant to FDA with response to questions.
Feb 7 01			**SUBMISSION** – with response to requests of Jan 22 and Jan 24 01.
Feb 7 01			**SUBMISSION** - with response to request from Dr. Boyd.
Feb 8 01	Feb 09 01		**FAX** – from FDA to Applicant with biopharm comments on report W-144128 (protocol WP 15511).
Feb 15 01			**FAX** – from Applicant to FDA with response to questions made on Feb 9 01.
Feb 16 01			**EMAIL** – from Applicant to FDA with Patient

CORRESPONDENCE LOG – APPLICATION PHASE

SUBMISSION TYPE AND NO.: NDA 21-304

PRODUCT NAME: Valcyte™ (valganciclovir HCl) 450 mg Tablets

DATE SENT	DATE RCVD	SUPP#	SYNOPSIS
			ID's.
Feb 16 01			**FAX** – from Applicant to FDA, Request for a teleconference to discuss Tradename
Feb 16 01			**LETTER** – from Applicant to FDA, Request for a teleconference to discuss Tradename
Feb 16 01			**LETTER** – from Applicant to FDA with additional copies of the proposed bottle label
Feb 19 01			**FAX** – from Applicant to FDA with Final draft of sponsor presentation slides
Feb 19 01			**LETTER** – from Applicant to FDA with Final draft of sponsor presentation slides
Feb 20 01			**EMAIL** – from Applicant to FDA notifying that a fax is being sent re Tradename.
Feb 20 01			**FAX** - from Applicant to FDA with Response to questions from January 26, 01
Feb 20 01			**LETTER** - from Applicant to FDA with Response to questions from January 26, 01
Feb 20 01			**LETTER** - from Applicant to FDA with Addendum to Clinical Study Report W-144125 (Study WV15376) and an Addendum Report to virology report 1000511 (Study WV15376)
Feb 22 01			**FAX** - from Applicant to FDA with Corrections to the response dated Feb 20, 01
Feb 22 01			**LETTER** - from Applicant to FDA with Corrections to the response dated Feb 20, 01
Feb 27 01			Hand delivery of diskettes to Tara Turner, Pharm D before the Advisory Committee meeting

CORRESPONDENCE LOG – APPLICATION PHASE

SUBMISSION TYPE AND NO.: NDA 21-304

PRODUCT NAME: Valcyte™ (valganciclovir HCl) 450 mg Tablets

DATE SENT	DATE RCVD	SUPP#	SYNOPSIS
Mar 05 01	Mar 05 01		**FAX** – from FDA to Applicant with Chemistry Comments
Mar 05 01	Mar 05 01		**FAX** – from FDA to Applicant with Labeling Comments
Mar 08 01			**LETTER** – from Applicant to DDMAC reviewers with draft promotional materials for review.
Mar 08 01			**LETTER** – from Applicant with stability report including 3 month data for the Patheon registration batches
Mar 09 01	Mar 09 01		**EMAIL** – from FDA to Applicant with draft label revisions
Mar 09 01	Mar 0901		**FAX** - from FDA to Applicant with draft label revisions
Mar 13 01			**LETTER** – from Applicant with stability report including 24 month stability data for the Oread lots
Mar 13 01			**FAX** – from Applicant to FDA with the proposed phase IV commitment
Mar 13 01			**LETTER** – from Applicant to FDA with the proposed phase IV commitment
Mar 13 01	Mar 13 01		**FAX** – from FDA to Applicant with Response to questions on the label
Mar 14 01			**LETTER** – from Applicant with response to Chemistry Comments dated Mar 05 01
Mar 14 01	Mar 14 01		**EMAIL** – from FDA to Applicant with a request re revised label
Mar 15 01			**EMAIL** – from Applicant to FDA regarding a missing FedEx package
Mar 15 01			**LETTER** - from Applicant with the response to

CORRESPONDENCE LOG – APPLICATION PHASE

SUBMISSION TYPE AND NO.: NDA 21-304

PRODUCT NAME: Valcyte™ (valganciclovir HCl) 450 mg Tablets

DATE SENT	DATE RCVD	SUPP#	SYNOPSIS
			labeling comments dated March 05 01
Mar 15 01			**FAX** – from Applicant to FDA with response to labeling comments dated March 05 01
Mar 15 01			**LETTER** – from Applicant with response to labeling comments dated March 09 01
Mar 15 01			**EMAIL** – from Applicant with response to labeling comments dated March 09 01
Mar 15 01			**FAX** - from Applicant with response to labeling comments dated March 09 01
Mar 15 01			**EMAIL** - from Applicant to FDA with Attachment 3 and response.
Mar 15 01			**LETTER** – from Applicant to Reviewers submitting the Interim Process Validation Report
Mar 20 01			**FAX** – from FDA to Applicant re PK labeling comments
Mar 20 01			**EMAIL** – from Applicant to FDA with Questions for clarification regarding PK labeling comments dated Mar 20 01
Mar 20 01			**LETTER** – from Applicant to Reviewers with Response to Chemistry Comments.
Mar 20 01			**FAX** – from Applicant to Reviewers with Response to Chemistry Comments.
Mar 20 01			**FAX** – from FDA to Applicant with Revised label and PPI
Mar 21 01			**EMAIL** – from FDA to Applicant with Micro Labeling comments
Mar 21 01			**FAX** – from FDA to Applicant with Micro Labeling comments

CORRESPONDENCE LOG – APPLICATION PHASE

SUBMISSION TYPE AND NO.: NDA 21-304

PRODUCT NAME: Valcyte™ (valganciclovir HCl) 450 mg Tablets

DATE SENT	DATE RCVD	SUPP#	SYNOPSIS
Mar 21 01			**EMAIL** – from Applicant to FDA re Topics for teleconference
Mar 21 01			**EMAIL** – from Applicant to FDA re Comments re Table 3 in Clinical Trial Section of PI
Mar 22 01			**FAX** – from FDA to Applicant with Phase 4 commitments
Mar 22 01			**FAX** – from FDA to Applicant with Post Marketing commitments
Mar 22 01			**LETTER** - from Applicant to Reviewers with Response to Labeling comments dated Mar 20 (General and PK) and Mar 21 01 (Microbiology) includes a diskette
Mar 22 01			**FAX** - from Applicant to FDA with Response to PPI Label Comments from Mar 20 01
Mar 22 01			**FAX** - from Applicant to Reviewers re Post Marketing Commitments
Mar 22 01			**LETTER** - from Applicant to Reviewers re Post Marketing Commitments
Mar 22 01			**EMAIL** - from Applicant to FDA with Roche comments on USPI
Mar 22 01			**EMAIL** - from Applicant to FDA with Roche comments on PPI
Mar 23 01			**FAX** - from Applicant to FDA with Microbiology References (the attachments are not included here; refer to NDA)
Mar 23 01			**EMAIL** - from Applicant to FDA re Table 3; Patient #0602
Mar 26 01			**EMAIL** – from FDA to Applicant re patient #0602

CORRESPONDENCE LOG – APPLICATION PHASE

SUBMISSION TYPE AND NO.: NDA 21-304

PRODUCT NAME: Valcyte™ (valganciclovir HCl) 450 mg Tablets

DATE SENT	DATE RCVD	SUPP#	SYNOPSIS
Mar 26 01			**EMAIL with text-** from FDA to Applicant with revised PPI (revisions by review team)
Mar 26 01			**EMAIL with attachment-** from FDA to Applicant with revised PPI (revisions by review team)
Mar 26 01			**FAX** - from FDA to Applicant with Microbiology comments
Mar 26 01			**EMAIL** - from Applicant to FDA with Roche response to Microbiology comment of Mar 26 01
Mar 26 01			**FAX** - from Applicant to FDA with Roche response to Microbiology comment of Mar 26 01
Mar 26 01			**LETTER** - from Applicant to FDA with Roche response to Microbiology comment of Mar 26 01
Mar 26 01			**EMAIL** - from Applicant to FDA with source for information for Zalcitabine and Trimethoprim
Mar 27 01			**EMAIL** - from FDA to Applicant with PK Labeling comments
Mar 27 01			**FAX** - from FDA to Applicant with PK Labeling comments
Mar 27 01			**EMAIL** - from Applicant to FDA re Ganciclovir oral profile Figure 1
Mar 27 01			**EMAIL** - from Applicant to FDA with Revised Label
Mar 27 01			**FAX** - from Applicant to FDA with Revised Label
Mar 27 01			**LETTER** - from Applicant to FDA with Revised Label
Mar 28 01			**EMAIL** - from FDA to Applicant re the Label
Mar 28 01			**EMAIL** - from Applicant to FDA re Valcyte

CORRESPONDENCE LOG – APPLICATION PHASE

SUBMISSION TYPE AND NO.: NDA 21-304

PRODUCT NAME: Valcyte™ (valganciclovir HCl) 450 mg Tablets

DATE SENT	DATE RCVD	SUPP#	SYNOPSIS
Mar 28 01			**EMAIL** - from Applicant to FDA with PI
Mar 28 01			**EMAIL** - from FDA to Applicant with label with PK changes highlighted
Mar 28 01			**EMAIL** - from Applicant to FDA with clean copy of the label and a copy in revision mode
Mar 28 01			**EMAIL** - from Applicant to FDA with Final Label
Mar 28 01			**LETTER** - from Applicant to Reviewers with Final Label
Mar 29 01			**EMAIL** - from Applicant to FDA with changes to the label including comment by Dr. Cvetkovich
Mar 29 01			**FAX** - from Applicant to FDA with Final Label including comments from Mar 29 01
Mar 29 01			**LETTER** - from Applicant to FDA with Final Label including comments from Mar 29 01
Mar 29 01			**FAX** - from FDA to Applicant with Approval Letter
Mar 29 01			**LETTER** - from FDA to Applicant with Approval Letter